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TREATMENT STRATEGIES FOR ESOPHAGEAL STRICTURE BEFORE OR AFTER CHEMORADIOTHERAPY FOR ADVANCED ESOPHAGEAL CANCER

MANABU MUTO, ATSUSHI OHTSU AND SHIGEAKI YOSHIDA

Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

ABSTRACT

Esophageal stricture due to advanced cancer is one of the serious complications of esophageal cancer as it causes dysphagia. A self-expandable metallic stent is easily inserted in such patients and provides immediate symptomatic relief of dysphagia. Alternatively, definitive chemoradiotherapy has demonstrated a significant improvement in local control and overall survival, and is now commonly used for not only unresectable esophageal cancer patients but also in resectable cases. However, little is known about its role in relief of dysphagia. Therefore, we reviewed our experience of patients with esophageal stricture who were treated with chemoradiotherapy. We expect that the findings in this article might be useful in future clinical practice.

Key words: esophageal stricture, chemoradiotherapy, self-expandable metallic stent, percutaneous endoscopic gastrostomy.

INTRODUCTION

Patients with locally advanced esophageal cancer sometimes develop an esophageal stricture, which is one of the serious complications of esophageal cancer as it causes dysphagia. Self-expandable metallic stents (EMS) have been used for palliation and provide immediate symptomatic relief of dysphagia.[1,2] Alternatively, definitive chemoradiotherapy (CRT) has demonstrated a significant improvement in local control and overall survival[3–6] and is now accepted as one of the standard treatments for esophageal cancer;[7,8] however, little is known about its role in relief of dysphagia.

Selection of treatment for patients with stricture due to untreated esophageal cancer

First, we should consider patients with newly diagnosed esophageal cancer with severe stricture at presentation. If they have unresectable T4 (TNM classification) tumors, how are those patients best managed? We know that EMS is easily deployed for such patients and resolves dysphagia promptly. However, it is only palliative therapy and does not provide a survival benefit. To evaluate the role of relief of dysphagia by CRT, we reviewed our experience of 51 patients with unresectable T4 esophageal cancer who were treated with definitive CRT. The CRT consisted of 60 Gy of external beam irradiation in 30 fractions concurrent with chemotherapy (5-fluorouracil (5FU) + cisplatin or nedaplatin). The ability to swallow was evaluated before and after completion of CRT and expressed as a dysphagia score: a score of 0 denoted complete dysphagia; (1) the ability to swallow only liquid; (2) the ability to eat semi-solids only; and (3) the ability to eat solid food. The results are shown in Figures 1 and 2. The dysphagia score improved in most patients. The median dysphagia score was 2 before CRT, and 3 after completion of CRT (Fig. 1). In addition, the complete response rate was 35% (18/51), and definitive CRT achieved a three-year survival rate of 26% (Fig. 2). These results indicate that definitive CRT provides not only symptomatic relief of dysphagia but also a chance of survival.

Correspondence: Manabu Muto, Division of Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan. Email: mmuto@east.ncc.go.jp

CRT for patients with malignant fistulae due to esophageal cancer

How are esophageal cancer patients with malignant fistulae best managed? Most physicians and surgeons believe that radiotherapy or CRT for the patients with malignant fistula is contraindicated, because it may worsen the fistula. We previously reported that malignant fistulae closed in 92% (11/12) of patients after the completion of CRT, and most of them had improved the dysphagia scores[6] (Fig. 3). While the median survival time (MST) of patients with fistulae has been reported to be one to six weeks, the MST of those treated by definitive CRT was 7 months in our previous study (Fig. 4). This indicates that definitive CRT provides a chance of closure of fistulae and improves the survival.

Risks of EMS combined with CRT

Data regarding the combination treatment of EMS placement with subsequent CRT for patients with esophageal stricture due to advanced cancer is quite limited. Recently, Nishimura *et al.* reported an important investigation on the placement of stents before or during radiotherapy to the patients with advanced esophageal cancer.[9] They gathered

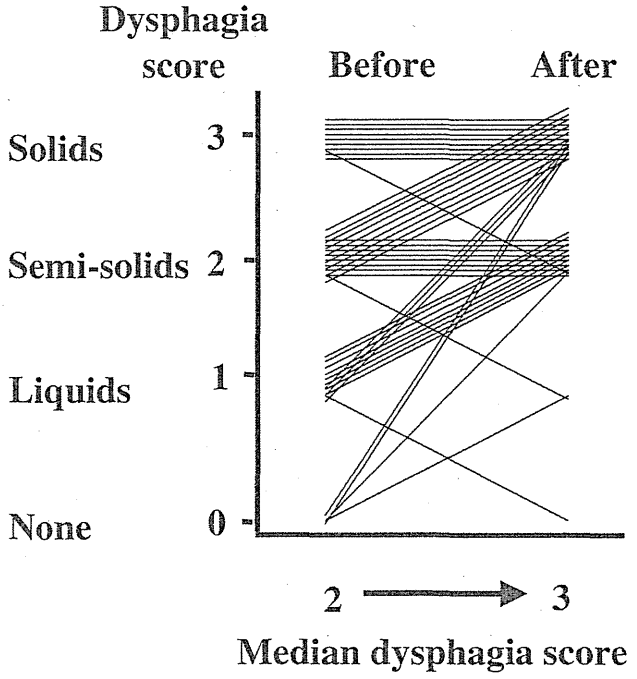

Fig. 1. Improvement of dysphasia score in the patients with esophageal stricture after completion of definitive chemoradiotherapy.

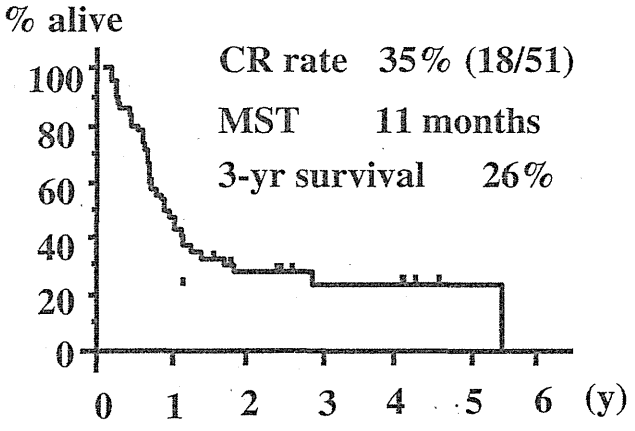

Fig. 2. Overall survival of the patients with T4 esophageal cancer treated with definitive chemoradiotherapy.

clinical data of 47 patients from 17 institutions in Japan. Covered metallic stents were used for 30 patients, uncovered metallic stents for 13 patients, plastic or silicon prosthesis for three patients, and an unknown type for one patient. Esophageal intubation was performed before the start of radiation for 23 patients and during the course of radiation for remaining 24 patients. The median total external beam radiotherapy dose was 60 Gy (6–70) and two-thirds of the patients received more then 50 Gy. Formation of or a worsening esophageal fistula occurred in 28% of such patients. Furthermore, possible treatment-related deaths were 21%. They concluded that patients with an esophageal stent introduced before or during radiotherapy have a high risk of life-threatening compli-

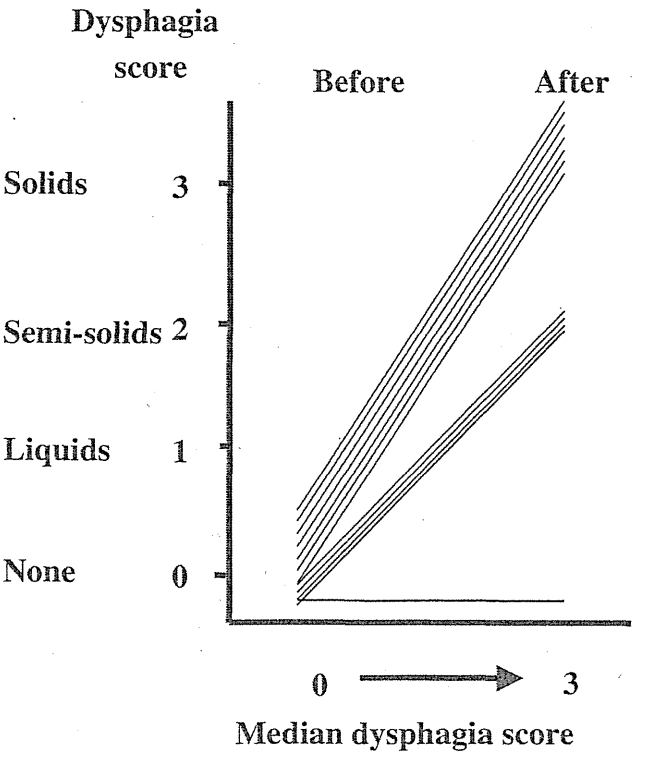

Fig. 3. Improvement of dysphasia scores in esophageal cancer patients with malignant fistula after completion of definitive chemoradiotherapy.

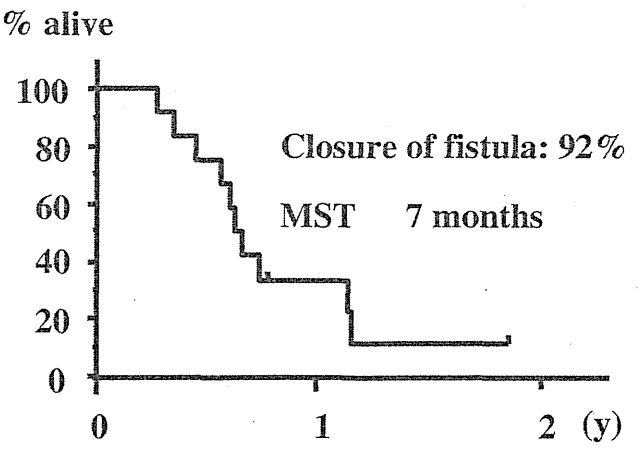

Fig. 4. Overall survival of esophageal cancer patients with malignant fistula treated with definitive chemoradiotherapy.

cations. Palliative stent placement should be delayed until radiotherapy or CRT appears to have failed, because a longer survival time is expected for patients with locally advanced esophageal cancer after CRT.

Risk of EMS placement for recurrent stricture after failure of CRT

Dysphagia due to recurrent stricture after failure of CRT means that the patient will suffer similarly to those with non-

Table 1. Self-expandable metallic stent placement for recurrent esophageal stricture after failure of radiotherapy and/or chemotherapy

Authors	Year	*n*	Rate of life-threatening complications	Does it increase the risk?
Kinsman K *et al.*[11]	1996	22	36%	Yes
Bethge N *et al.*[12]	1996	13	23%	Yes
Siersema PD *et al.*[13]	1998	20	43%	Yes
Raijman I *et al.*[14]	1997	39	8%	No
Muto M *et al.*[10]	2001	13	54%	Yes
Kaneko K *et al.*[15]	2002	12	17%	Yes
Sumiyoshi T *et al.*[16]	2003	22	High	Yes

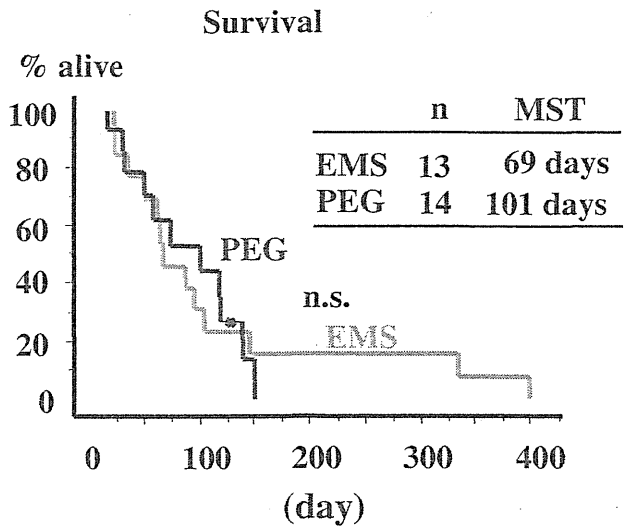

Fig. 5. Comparison of the overall survival between the patients inserted with a self-expandable metallic stent and those treated by percutaneous endoscopic gastrostomy.

treated esophageal cancer at presentation. Therefore, the main goal of palliative treatment is to relieve dysphagia even in such patients. However, it has been suggested that prior radiotherapy to the EMS placement may be associated with an increased rate of complications. We have also reported that although EMS after failure of definitive CRT improved the dysphagia score, it increased the risk of life-threatening pulmonary complications.[10] To date, many investigators have also reported the results of EMS placement for recurrent esophageal stricture after failure of radiotherapy or CRT.[11–16] We have summarized the rates of life-threatening complication in their reports (Table 1) and most concluded that EMS after failure of radiotherapy or CRT increased the rate of complications.

How should patients with recurrent dysphagia be managed after failure of CRT?

We compared the efficacy and safety between EMS and percutaneous endoscopic gastrostomy (PEG) after failure of CRT. The types of EMS deployed are summarized in Table 2. A covered stent was used for eight patients and a non-covered type was used for five. A 'one step button' was used for all PEG procedure. As for clinical events, the incidence of high fever, severe chest pain that required analgesics, and inflammation were significantly higher in the EMS group (Table 3). Survival was not different between the two groups (Fig. 5). Therefore, to improve the patients' quality of life (QOL), it seems that PEG is more feasible and safer than EMS placement.[17]

Table 2. Self-expandable metallic stent (EMS) devices and percutaneous endoscopic gastrostomy used for recurrent dysphagia after failure of definitive chemoradiotherapy

		n	Total
EMS			
Ultraflex (covered)		7	
Ultraflex (non-covered)		2	
Wall (covered)		1	
Wall (non-covered)		1	
Z-stent		2	13
PEG			
One step button	18Fr	4	
	24Fr	10	14

Table 3. Comparison between self-expandable metallic stent (EMS) and percutaneous endoscopic gastrostomy (PEG) after failure of definitive chemoradiotherapy

	EMS ($n = 13$)	PEG ($n = 14$)
High fever*	11 (85)	3 (21)
Severe pain*	8 (73)	2 (14)
CRP ↑	11 (85)	8 (57)
Pneumonia/Mediastinitis*	7 (54)	0 (0)
Peritonitis	0 (0)	1 (7)
Hospital stay (Median day, range)	28 (10–106)	13 (6–36)

(%); * $p < 0.005$.

CONCLUSION

Although SEM placement provides effective palliation for patients with esophageal stricture due to advanced cancer, long-term survival is not expected by this modality. In contrast, definitive CRT provides not only symptomatic relief of dysphagia but also a chance of survival. Therefore, we should

carefully select the treatment for such patients in consideration of the advantages for their QOL and survival.

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ORIGINAL REPORT

Comparison of the Efficacy, Toxicity, and Pharmacokinetics of a Uracil/Tegafur (UFT) Plus Oral Leucovorin (LV) Regimen Between Japanese and American Patients With Advanced Colorectal Cancer: Joint United States and Japan Study of UFT/LV

K. Shirao, P.M. Hoff, A. Ohtsu, P.J. Loehrer, I. Hyodo, S. Wadler, R.G. Wadleigh, P.J. O'Dwyer, K. Muro, Y. Yamada, N. Boku, F. Nagashima, and J.L. Abbruzzese

From the Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo; Division of Gastrointestinal Oncology/Digestive Endoscopy, National Cancer Center Hospital East, Chiba; Department of Internal Medicine, National Shikoku Cancer Center, Ehime, Japan; Division of Hematology & Medical Oncology, Department of Medicine, Weill Medical College of Cornell University, Ithaca, NY; Oncology Section, Department of Veterans Affairs Medical Center, Washington, DC; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; Section of Hematology & Oncology, Indiana University Cancer Center and The Walther Cancer Institute, Indianapolis, IN.

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Address reprint requests to Kuniaki Shirao, MD, Division of Gastrointestinal Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan; e-mail: kshirao@gan2.ncc.go.jp.

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ABSTRACT

Purpose
To compare the efficacy, toxicities, and pharmacokinetics of an oral regimen consisting of uracil/tegafur (UFT) and leucovorin (LV) between Japanese patients and patients in the United States with previously untreated metastatic colorectal cancer.

Patients and Methods
Forty-four Japanese patients and 45 patients in the United States were enrolled in concurrent nonrandomized phase II trials. UFT 300 mg/m^2/d and leucovorin 75 mg/d were administered orally for 28 days followed by a 7-day rest period. The total daily dose of each drug was divided into three equal doses. Treatment was repeated every 5 weeks until disease progression. Blood samples for the pharmacokinetic study were obtained after the initial dose on day 1 of the first course.

Results
The response rate for the Japanese patients and the patients in the United States was 36.4% (95% CI, 22.4% to 52.2%) and 34.1% (95% CI, 20.5% to 49.9%), respectively. The only major toxicity was diarrhea, and other toxicities were mild in both populations. The incidence of grade 3 or higher diarrhea in the Japanese and Americans was 9% and 22%, respectively. Although the area under the curve and maximum concentration of fluorouracil were found to be slightly higher in the Japanese patients than the patients in the United States, and area under the curve–adjusted body surface area appeared to be comparable between the two groups.

Conclusion
The efficacy and pharmacokinetic parameters of UFT and LV are comparable in Japanese and American patients; however, a difference in toxicity profile, specifically diarrhea, was noted. This oral regimen of UFT and LV is considered to have similar activity against metastatic colorectal cancer and to have acceptable toxicity in patients in both countries.

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INTRODUCTION

Colorectal cancer is the second most frequent cause of cancer deaths in the United States and most European countries, and its incidence has recently been increasing in Japan, where the number of deaths attributed to colorectal cancer now ranks third after lung cancer and gastric cancer. Colorectal cancer is therefore a major health problem worldwide, and the median survival time of patients with metastatic colorectal cancer treated with supportive care alone is approximately 4 to 6 months.[1] Systemic chemotherapy has recently been shown to prolong survival time, and median survival times now range from 17 to 21 months.[2,3]

Combination of irinotecan with fluorouracil (FU)/leucovorin (LV) as a first-line treatment for metastatic disease has

produced a survival benefit,[2,4] but recently there has been concern about the toxicity of the weekly bolus combination.[5] A randomized cooperative group study has yielded preliminary data that supports the continued role of intravenous(IV) FU and LV as the backbone of treatment for metastatic colorectal cancer.[6]

Uracil/tegafur (UFT) is a preparation composed of tegafur and uracil in a molar ratio of 1:4. Tegafur is a prodrug of FU and is mainly converted to FU in the liver.[7] In preclinical studies, the coadministration of uracil with tegafur enhanced the antitumor activity achieved with tegafur alone. Uracil strongly inhibits the degradation of FU to 2-fluoro-beta-alanine, thereby increasing the concentration of FU in plasma without increasing the toxicity resulting from 2-fluoro-beta-alanine.[8] LV is used to modulate FU biochemically, and has been widely adopted for the treatment of advanced colorectal cancer. Given the extensive use of LV with FU, the combination of UFT with oral LV was assessed for treatment of colorectal cancer, and administration schedules of UFT and oral LV were developed in phase I and II studies.[9-12] Those studies showed that the combination was very effective against metastatic colorectal cancer and had an acceptable safety profile. A randomized cross-over trial in advanced colorectal cancer showed that oral UFT/LV compared favorably with IV FU/LV in terms of toxicity and patient's preference, and that it prolonged FU exposure to a level comparable to the exposure achieved with continuous IV FU administration.[13]

The results of two large phase III studies on the UFT/LV regimen in Western countries were reported recently and demonstrated similar survival between IV FU/LV and UFT/LV in Western patients with metastatic colorectal cancer.[14,15] UFT was developed in Japan and is commonly used there, and the Japanese experience has demonstrated that UFT is well tolerated and displays evidence of antitumor activity in a variety of solid tumors.[16] Although several dosage regimens of UFT alone have been tried in colorectal cancer in Japan, there have been few studies on the combination of UFT plus LV in Japan.

We conducted the present study to determine whether the results of these phase III studies could be extrapolated to Japanese patients. If it showed equality of efficacy, safety, and pharmacokinetics in both Japanese and American patients, then the results of the Western phase III trials could be extrapolated to Japanese patients. This study was designed as an identical nonrandomized phase II analysis to evaluate the impact of ethnic factors on the efficacy and safety of a particular dosage and dose regimen in American and Japanese patients. The end point of the study was estimation of the efficacy, safety, and pharmacokinetic parameters of UFT/LV in American and Japanese patients with previously untreated metastatic colorectal cancer.

PATIENTS AND METHODS

Patient Selection

Patients had to be either Japanese or American nationals. The patients enrolled at the Japanese sites had to have been born in Japan and have lived more than 75% of their life in Japan, including the 2 years before enrollment. Patients enrolled at the US sites had to have been born in the United States and have lived more than 75% of their life there, including the 2 years before enrollment. Patients in both countries were entered into the study only if they fulfilled the following eligibility criteria: (1) histologic confirmation of colorectal carcinoma, (2) inoperable metastatic disease or recurrent metastatic disease after surgery, (3) measurable lesions, (4) age $\geq$ 20 years but $\leq$ 75 years, (5) performance status (PS) $\leq$ 2 on the Eastern Cooperative Oncology Group (ECOG) scale, (6) no prior chemotherapy for advanced disease (prior adjuvant chemotherapy for colorectal cancer must have been completed at least 6 months before enrollment), (7) adequate bone marrow function (absolute granulocyte count $\geq$ 1,500/μL and platelet count $\geq$ 100,000/μL), (8) adequate liver function (serum bilirubin level 1.5 mg/dL and serum transaminase levels $\leq$ 100 U/L), (9) adequate renal function (serum creatinine level $\leq$ 1.5 mg/dL), (10) no other severe medical conditions, (11) no other active malignancies, (12) no pregnant or breast-feeding women, and (13) provision of written informed consent.

Treatment Schedule

The dose of UFT was 300 mg/m^2/d for 28 days followed by a 7-day rest period. The total daily dose was divided into three doses administered orally every 8 hours (at approximately 7 AM, 3 PM, and 11 PM). UFT (Taiho Pharmaceutical Ltd, Tokyo, Japan) was supplied in the form of 100-mg capsules (100 mg tegafur). The daily dose of UFT was rounded up or down to the nearest 100 mg. If the capsule dose could not be divided equally, the highest dose was administered in the morning and the lower doses in the evening. Leucovorin (Lederle Laboratories, Wayne, NJ) was supplied as 25-mg tablets and administered orally at a dose of 75 mg/d. The total daily dose was divided equally into three doses administered concurrently with UFT. Patients consumed no food for an hour before and after taking the drugs. A course of therapy was defined as 28 consecutive days of treatment followed by a 7-day rest period, and courses were repeated every 5 weeks until disease progression or severe toxicity was observed. Patient compliance was verified by counting the remaining pills at the end of each course of treatment. Treatment was interrupted for grade 3 or higher granulocytopenia or thrombocytopenia, or grade 2 to 4 nonhematologic toxicity. If treatment was discontinued because of a grade 2 nonhematologic toxicity, UFT and LV were resumed at the same doses when the toxicity had completely resolved. Whenever grade 3 or 4 toxic effects occurred, the UFT dose was reduced by 50 mg/m^2/d in subsequent courses, but the dose of LV remained at 75 mg/d.

Evaluation

Patients were evaluated by appropriate investigations, including physical examination, chest x-ray, and computed tomographic scans of the abdomen and chest, before entry into the study to determine the extent of disease. A complete blood cell count, liver function tests, renal function tests, and urinalysis were performed at least once every 2 weeks during treatment. Appropriate investigations were repeated as necessary to evaluate the sites of marker lesions before every course or every other course.

The tumor response of the lesions was evaluated according to WHO criteria.[17] National Cancer Institute common toxicity criteria were applied to evaluate the toxicity of this therapy.[18] The eligibility and suitability of the subjects for assessment and their response to treatment were reviewed extramurally.

Pharmacokinetics

On day 1, blood specimens were obtained immediately before drug administration and at 0.25, 0.5, 1, 1.5, 2, 3, 5, and 8 hours after drug administration. They were collected in heparinized tubes and centrifuged in a refrigerated centrifuge, and the plasma obtained was frozen at −20°C until analysis.

Concentrations of tegafur (FT) were determined by a validated high-performance liquid chromotography (HPLC) assay with ultraviolet detection based on the method reported by Muranaka et al.[19] A validated gas chromatographic-mass spectrometric assay method was used to quantitate FU and uracil in the plasma samples. The assay method used was based on a method published previously for FU[20] and was modified to include simultaneous quantitation of uracil as reported by Muranuka et al.[19] LV and 5-methyl tetrahydrofolate (5-MTHF) were determined by validated HPLC methods that were modifications of methods reported previously.[21,22] LV and 5-MTHF were extracted from plasma as described by Etienne et al[21]; however, LV was resolved from endogenous interference by gradient HPLC (mobile phase A, 40% acetonitrile-50% methanol in 25 mmol/L KH_2PO_4 [pH 2.3]; mobile phase B, 25 mmol/L KH_2PO_4 [pH 2.3]), and 5-MTHF was resolved from endogenous interference by isocratic HPLC with a mobile phase consisting of 5% acetonitrile-50% methanol in 25 mmol/L KH_2PO_4 (pH 2.3). Both LV and 5-MTHF were detected at 310 nm.[22]

For FT, FU, and uracil, the standard curves were linear ($R^2 > 0.991$) over the concentration range of 50 to 20,000, 1 to 5, and 20 to 5,000 ng/mL, respectively. Based on the analysis of quality control samples, the accuracy was −0.9% to 3.4% and the inter- and intrarun precision was 6.0% to 7.9% of the assays for FT; 5.7% to 11.0% and 2.0% to 8.6% for FU; and 2.8% to 8.0% and 1.2% to 8.7% for uracil. For both LV and 5-MTHF, the standard curves were linear ($R^2 > 0.992$) over the concentration range of 50 to 2,000 ng/mL; the accuracy was 1.5% to 3.0%, and the inter- and intrarun precision was 5.9% to 8.7% of the assay for LV, and 1.8% to 3.3% and 4.5% to 7.8% for 5-MTHF, respectively.

The plasma concentration-time data following administration for five analyses were analyzed by a noncompartmental method using the computer program WINNonlin (version 3.1; Pharsight Co, Apex, North Carolina). The peak plasma concentration (C_{max}) and the time to reach the peak concentration (T_{max}) were recorded directly from the experimental observations. The area under the plasma concentration-time curve (AUC) from time 0 to T, AUC_{0-T}, where T is the time of the last measurable concentration, was calculated by the trapezoidal method. No weighting factor was used, and the slope of the terminal phase of the plasma profile, K, was determined by log-linear regression of at least three data points, which yielded a minimum mean square error. The absolute value of K was used to estimate the terminal half-life ($t_{1/2}$) according to the formula $t_{1/2} = \ln 2/K$. AUC from time 0 to infinity, AUC_{0-inf}, was determined by summing the areas from time 0 to the time of the last measured concentration, calculated using conventional trapezoidal and log-trapezoidal methods, and the extrapolated area. The extrapolated area was determined by dividing the final concentration by the slope of the terminal log-linear phase. Since a terminal log-linear phase was not identified in a minority of the patients, the $t_{1/2}$ and AUC_{0-inf} values of these patients could not be calculated.

Statistical Methods

Response rates of metastatic colorectal cancer between 16.6% to 21.5% for UFT alone and between 18% and 43% for UFT plus LV have been reported in some phase II studies. The sample size in this study was calculated based on a target activity level of 31.5% and minimum activity level of 20%, to ensure the lower limit of the 90% CI, and thus the number of patients required in each country was 44. Time to progression was measured from the start of treatment to the date of progression. Progression time was censored at the close out date if progressive disease was not observed.

The equivalence of AUC and C_{max} in analyses was concluded if the 90% CI with a power of 80% for difference of logarithmic means between Japanese and American patients was entirely within the range of −0.36 to 0.36.

This trial was approved by the institutional review board of the clinical oncology program at all hospitals participating in this study.

RESULTS

Eighty-nine patients with advanced metastatic colorectal carcinoma were entered onto the trial between November 1998 and September 2000. Forty-four patients were entered in Japan, and all were assessable for toxicity and response. Forty-five patients were entered in the United States, and 44 were assessable for response. One patient in the United States was judged ineligible because no target lesions were available. The 44 patients in the United States consisted of 30 white patients, four Hispanic patients, and 10 black patients.

The characteristics of the eligible patients are listed by country in Table 1. Almost all patients in both groups had good performance status. Almost all patients in both groups had undergone surgery, and five (11%) Japanese patients and 10 (23%) patients in the United States (hereafter, "American patients") had received FU-based adjuvant chemotherapy. The characteristics of the 88 eligible Japanese and American patients were matched for age, sex, performance status, and prior therapy.

The actual daily doses of UFT according to body-surface area (BSA) are shown in Table 2. Because the mean BSA of the American patients was larger (mean: American, 1.92 m^2; Japanese, 1.57 m^2), the median actual daily dose of UFT received by the American patients was 600 mg, as opposed to 500 mg by the Japanese patients. The median number of courses of treatment was four in both countries.

Response

All 44 Japanese patients had measurable lesions. Fourteen patients had a partial response, and two patients had a complete response (response rate, 36.4%; 95% CI, 22.4% to 52.2%; Table 3). Two patients were not assessable because of early withdrawal due to toxicity. The response rate by metastatic site was 35% (six of 17 patients) in the lung, 30% (eight of 27 patients) in the liver, and 18% (two of 11

Table 1. Characteristics of Eligible Patients

	Japan (n = 44)		United States (n = 44)*	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	59		60	
Range	26-73		44-88	
Sex				
Male	26	59	29	66
Female	18	41	15	34
PS (ECOG)				
0-1	42	95	44	100
2	2	5	0	0
Primary lesions				
Colon	24	55	34	77
Rectal	20	45	10	23
Prior therapy				
Surgery	43	98	44	100
Adjuvant chemotherapy	5	11	10	23
Radiotherapy	0	0	4	9
Others	1	2	2	5
Body surface area, m^2				
Mean	1.57		1.92	
Range	1.19-1.92		1.53-2.63	

Abbreviations: PS, performance status; ECOG, Eastern Cooperative Oncology Group.
*Race/ethnicity: white patients, 30 (68%); Hispanic patients, four (9%); black patients, 10 (23%).

Table 3. Objective Response

	Japan (n = 44)	United States (n = 44)
Complete response	2	0
Partial response	14	15
Stable disease	11	18
Progressive disease	15	8
Not assessable	2	3
Overall response rate	16/44	15/44
%	36.4	34.1
95% CI	22.4 to 52.2	20.5 to 49.9

patients) in the lymph nodes. Of the 44 American patients with measurable metastatic lesions, 15 patients had partial responses, and there were no complete responses (response rate, 34.1%; 95% CI, 20.5% to 49.9%; Table 3). Three patients were not evaluated because of early withdrawal due to toxicity, early death as a result of disease progression, and a target lesion that was too small. The response rate by metastatic site was 71% (five of seven patients) in the lung, 24% (eight of 34 patients) in the liver, and 25% (two of eight patients) in the lymph nodes.

The median time to progression at the close of this trial (August 2001) was 127 days (range, 21 to 703+ days) among the Japanese patients and 142 days (range, 19 to 512 days) among the American patients.

Toxicity

Forty-four Japanese patients and 45 American patients were assessable for toxicity. Table 4 shows the highest grade of toxicities during all treatment courses according to patient. Although the incidence of grade 3 and 4 hematologic toxicities in the American patients was almost the same as in the Japanese patients, the incidence of all grades of thrombocytopenia was higher in the American patients than in the Japanese patients. Diarrhea occurred in 38.6% of the Japanese and 68.9% of the American patients ($P = .006$). The incidence of grade 3 and 4 diarrhea was also higher in the American patients (22.2%) than in the Japanese patients (9.1%). Five American patients exhibited grade 3 or 4 dehydration due to diarrhea. All-grade and grade 3 and 4 nausea and vomiting were higher in the American patients than in the Japanese patients. However, the incidences of the grade 3 or 4 toxicities were not high, even among the American patients. All-grade and grade 3 or 4 stomatitis/mucositis occurred more often in the Japanese patients (34.1% and 4.5%, respectively) than in the American patients (17.8% and 0%, respectively). Hand-foot syndrome

Table 2. Body Surface Area and UFT Dose

			Japan (n = 44)		United States (n = 44)			
BSA (m^2)	Daily Dose of UFT (mg)	Divided Doses (mg)	No. of Patients	%	No. of Patients	%	No. of Patients for Pharmacokinetic Study (n = 43)	%
BSA ≤ 1.49	400	200-100-100	15	34	0	0	0	0
1.5 ≤ BSA ≤ 1.83	500	200-200-100	26	59	17	39	18*	42
1.84 ≤ BSA ≤ 2.16	600	200-200-200	3	7	20	45	19	44
2.17 ≤ BSA ≤ 2.5	700	300-200-200	0	0	5	11	4	9
2.51 ≤ BSA	800	300-300-200	0	0	2	5	2	5

Abbreviations: UFT, uracil/tegafur; BSA, body surface area.
*One patient, who was judged ineligible because no target lesions were available, was added for pharmacokinetic analysis.

Table 4. Toxicity

	Japan (n = 44)		United States (n = 45)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Anemia	47.7	4.5	31.1	2.2
Neutropenia	34.1	0	22.2	0
Thrombocytopenia	6.8	2.3	31.1	0
Diarrhea	38.6	9.1	68.9	22.2
Nausea	29.5	0	64.4	4.4
Vomiting	18.2	0	31.1	4.4
Stomatitis/mucositis	34.1	4.5	17.8	0
Hand-foot syndrome	0	0	2.2	0
Bilirubin	59.1	4.5	46.7	4.4
AST	38.6	2.3	30.6	5.6
ALT	38.6	4.5	33.3	0

was rarely observed in either group. The incidence of grade 3 and 4 abnormal bilirubin and AST and ALT values was almost the same in both groups (2.3% to 5.6%).

Almost all grade 3 or 4 toxicity occurred before the end of the second course of treatment. All 14 patients (Japan, three patients; United States, 11 patients) in both countries who exhibited any grade 3 and 4 toxicity were hospitalized for treatment. Two Japanese patients discontinued the UFT/LV regimen because of grade 3 hyperbilirubinemia, grade 4 elevation of AST/ALT, and grade 2 transient cerebral ischemia that was judged to have no relation to the drug. One American patient discontinued treatment because of grade 3 diarrhea with dehydration. However, it was not deemed necessary to discontinue treatment in any of the other patients who experienced grade 3 or 4 toxicities. These patients were able to continue treatment after a temporary interruption or decrease in the dose of the drug. Of the 193 courses administered, 183 (95%) were given at 75% or more of the protocol-defined dose of UFT among the Japanese patients. Of the 221 courses administered, 210 (95%) were given at 75% or more of the protocol-defined dose of UFT among the American patients. There were no treatment-related deaths. This regimen was well tolerated and could be repeated as planned in both countries.

Pharmacokinetics

Blood specimens for pharmacokinetic analysis were available from 44 patients in Japan and 43 patients in the United States, and a summary of the results along with the numbers of patients available for each parameter is provided in Table 5. A patient was judged nonassessable for pharmacokinetic analysis if three or more blood specimens were missing.

For each parameter, the 90% CIs for difference of logarithmic means between Japanese patients and American patients are shown Table 6. The $AUC_{0\text{-}8\ hours}$ and C_{max} for each compound, except for LV, were not equivalent with a power of 80% between the countries. The mean $AUC_{0\text{-}8\ hours}$ and C_{max} for FT and uracil in the Japanese patients tended to be higher than in the American patients. The same tendency was also observed with regard to FU, which is an active form of UFT (Table 5). The mean $AUC_{0\text{-}8\ hours}$ and C_{max} of FU in the Japanese patients were 1.36 and 1.61 times as large as in the American patients. The plasma FU over time curves of both groups are shown in Figure 1. The mean $AUC_{0\text{-}8\ hours}$ and C_{max} for LV were similar between the countries. The plasma LV over time curves of the Japanese and American patients are shown in Figure 2. Furthermore, the mean $AUC_{0\text{-}8\ hours}$ and C_{max} for 5-MTHF, which is a metabolic product of LV, also tended to be higher in the Japanese patients than the American patients (Table 5).

Data was obtained from blood specimens collected during the 8 hours after a single dose of UFT/LV in the morning on day 1. As shown in Table 2, the total daily dose of UFT was decided according to the patient's BSA, but the morning dose of UFT was not (the morning dose of UFT was the same in all patients receiving 400 to 600 mg as the total daily dose). We therefore examined the AUC of FU according to BSA (Fig 3). The subjects consisted of 81 patients (Japanese, 44 patients; American, 37 patients) who were administered 200 mg as the initial dose of UFT on day 1 of the first course. In the group with a BSA from 1.50 to 1.83 m^2, the AUCs of the 18 American patients were distributed from 31.0 ng · h/mL to 494.1 ng · h/mL, and the AUCs of the 26 Japanese patients (52.2 to 418.2 ng · h/mL) were distributed within the American patients' range. In addition, in the group with a BSA from 1.84 to 2.16 m^2, a similar tendency was observed. The distribution of the AUCs for FU were similar among patients from both countries within the same BSA range. The AUCs of uracil- and LV-adjusted BSA also showed the same findings between the countries. Therefore, the pharmacokinetic parameters of UFT/LV appear to be comparable between Japanese and American patients.

DISCUSSION

Two large phase III studies were recently performed to compare an oral regimen of UFT and LV with conventional intravenous FU/LV therapy in patients with previously untreated metastatic colorectal carcinoma.[14,15] In both trials, the oral UFT/LV provided a safer, more convenient alternative to the standard bolus intravenous FU/LV regimen for metastatic colorectal cancer and resulted in similar survival. These large trials were performed in Western countries only, and thus we conducted the present study to determine whether the results of those phase III studies could be extrapolated to Japanese patients. The significance of this study lies in its comparison between patients living in

Table 5. Pharmacokinetic Parameters After Administration of UFT and LV

	$AUC_{0\text{-}8h}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
FT				
Japan				
Mean	41,063.2	9,158.7	0.8	6.5
SD	10,376.9	1,910.1	0.4	1.8
No. of available patients	44	44	44	44
United States				
Mean	23,857.8	5,470.7	1.3	5.4
SD	7,469.2	2,013.7	1.0	1.3
No. of available patients	43	43	43	40
Uracil				
Japan				
Mean	5,989.5	6,867.2	0.8	0.2
SD	3,255.1	3,772.3	0.4	0.1
No. of available patients	44	44	44	39
United States				
Mean	3,610.6	3,409.2	1.2	0.2
SD	3,218.7	3,305.3	0.8	0.1
No. of available patients	39	43	43	24
FU				
Japan				
Mean	223.1	245.0	0.7	0.3
SD	154.8	192.6	0.4	0.1
No. of available patients	44	44	44	44
United States				
Mean	164.0	152.2	1.1	0.6
SD	118.4	154.2	0.9	0.8
No. of available patients	43	43	43	41
LV				
Japan				
Mean	2,659.8	473.6	2.2	7.0
SD	1,156.5	214.0	0.6	1.9
No. of available patients	44	44	44	44
United States				
Mean	2,241.2	436.3	2.3	7.7
SD	942.2	293.1	1.1	2.6
No. of available patients	42	43	43	38
5-MTHF				
Japan				
Mean	2,046.7	468.0	2.3	3.1
SD	889.7	193.0	0.9	1.4
No. of available patients	43	44	44	36
United States				
Mean	1,498.5	337.8	2.8	3.9
SD	544.9	116.4	1.7	1.3
No. of available patients	37	43	43	26

Abbreviations: UFT, uracil/tegafur; LV, leucovorin; AUC, area under the curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration; $t_{1/2}$, half-life; FT, tegafur; SD, standard deviation; FU, fluorouracil; 5-MTHF, 5-methyl tetrahydrofolate.

two different countries, not in comparisons between patients of different races. This is the only trial in the literature to compare the efficacy, toxicity, and pharmacokinetics of UFT/LV between patients in two different countries.

The response rate in this trial was 36.4% in the Japanese patients and 34.1% in the American patients. The patient characteristics in both groups were almost identical, and the response rates were very similar, suggesting no difference between Japanese and American patients in regard to the efficacy of a combination of UFT and LV. These response rates are also compatible with the results (response rate, 18% to 43%) of other phase II studies of UFT/LV for colorectal cancer in Western countries.[11,12,23-27] The response rates in this trial and other phase II trials of UFT/LV were generally higher than with UFT alone in metastatic colorectal cancer in Japan (21.5%; 14 of 65 patients)[16] and the United Kingdom (16.6%; six of 36 patients).[28] However, the doses, schedules, eligibility criteria, and response criteria in the

Table 6. 90% CI for Difference in Logarithmic Means of Each Pharmacokinetic Parameter Between Japanese and Patients in the United States

Compound	PK Parameter (ng·h/mL)	Difference From Logarithmic Mean	90% CI
FT	AUC_{0-8}	0.5678	0.4601 to 0.6756
	C_{max}	0.5677	0.4529 to 0.6825
FU	AUC_{0-8}	0.3906	0.1293 to 0.6519
	C_{max}	0.7193	0.3722 to 1.0664
Uracil	AUC_{0-8}	0.7598	0.4515 to 1.0680
	C_{max}	1.0602	0.7145 to 1.4060
LV	AUC_{0-8}	0.1795	0.0265 to 0.3324
	C_{max}	0.1665	−0.0143 to 0.3472
5-MTHF	AUC_{0-8}	0.2762	0.1250 to 0.4275
	C_{max}	0.2899	0.1528 to 0.4270

Abbreviations: PK, pharmacokinetic; FT, tegafur; AUC, area under the curve; C_{max}, maximum concentration; FU, fluorouracil; LV, leucovorin; 5-MTHF, 5-methyl tetrahydrofolate.

trials differed, rendering a comparison of efficacy difficult. Nevertheless, the data support addition of the effect of LV to UFT, the same as with FU and LV, and this additional effect appears to be the same in different countries.

The incidence and degree of toxicity did not differ much between the countries, except for gastrointestinal toxicities and thrombocytopenia. The incidences of all grades of diarrhea, nausea and vomiting, and grade 3/4 diarrhea were higher in the American patients than in the Japanese patients. McCollum et al[29] have reported that treatment-related toxicity differs between the black and white patients receiving FU-based treatment, with white patients experiencing statistically significantly higher rates of diarrhea, nausea and vomiting, and stomatitis. The same tendency, except for stomatitis, was also observed among American patients in the present study. In particular, for diarrhea, the incidence of grade 3/4 diarrhea was 29% (nine of 31 patients) in the white patients, 0% (zero of 10 patients) in the black patients, and 25%(one of four patients) in the Hispanic patients. This difference in the incidence and degree of diarrhea between the Japanese and American patients in our study may be a reflection of racial/ethnic differences, although this has not been verified. However,

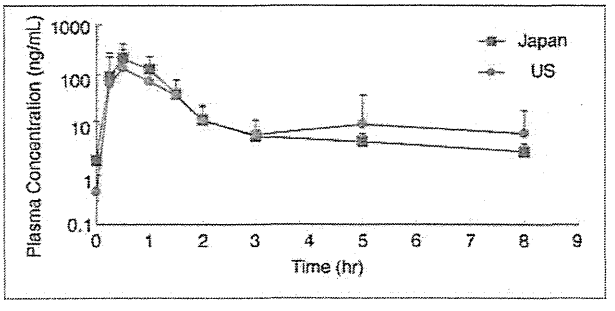

Fig 1. Plasma fluorouracil concentration versus time curve.

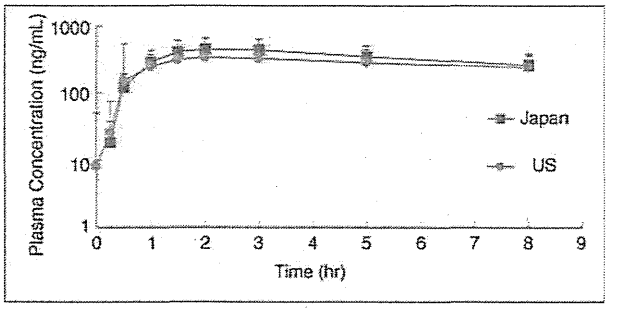

Fig 2. Plasma leucovorin concentration versus time curve.

diarrhea was manageable with antidiarrheal drugs or by temporary interruption of UFT/LV, and few patients in either group had to cease treatment because of diarrhea. Furthermore, a difference in the incidence of thrombocytopenia between the two countries was observed in the present study, although McCollum et al[29] reported no difference in thrombocytopenia according to race. However, in our trial, the grade was 1 for all American patients in which the incidence of thrombocytopenia was higher. Moreover, the mean nadir of thrombocytes between the countries did not differ (Japanese patients, 189,000/μL; American patients, 198,000/μL). Therefore, no significant difference in thrombocytopenia was apparent between the countries. UFT administration is only rarely complicated by hand-foot syndrome,[13-15] and similarly was rare in both groups in this trial. Although some differences in toxicities in both countries were observed in this trial, the incidence and degree of toxicities in both countries were mostly consistent with the results of the other phase II trials of UFT/LV.[11,12,23-27]

The mean AUC and C_{max} of FT and uracil in the present study were slightly higher in the Japanese patients than the American patients, and the AUC and C_{max} of FU, which is an active form of UFT, were also slightly higher in the Japanese patients than the American patients. The mean

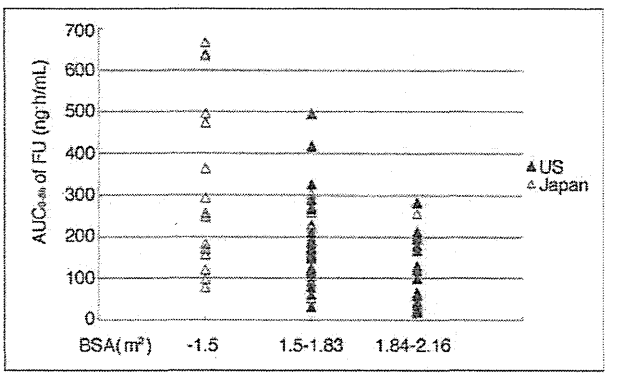

Fig 3. Area under the curve (AUC_{0-8h}) of fluorouracil (FU) according to body-surface area (BSA).

AUC values of FU in two other studies designed administering UFT 200 mg plus LV 30 mg in Western patients were 96.0[30] and 118 ng·h/mL,[31] respectively. Moreover, Borner et al[13] reported that the mean AUC value of FU on day 8 after administration of oral UFT 300 mg/m^2/d plus oral LV 90 mg/d to European patients was 113 μmol/L × min (244.8 ng·h/mL). The actual values for the mean AUC of FU obtained in those studies are similar to our data in American patients (164.0 ± 118.4 ng · h/mL) and similar to the results obtained in the Japanese patients (223.1 ± 154.8 ng·h/mL) in the present trial. Bolus intravenous FU has been reported to result in a significantly higher AUC and C_{max} of FU, indicating higher FU exposure than with oral UFT, and large phase III studies have confirmed higher toxicity and equal efficacy of intravenous FU in comparison to oral UFT.[14,15] These findings indicate that high FU exposure may not be necessary for tumor response, but may translate into toxicity.

We performed an analysis of covariance on the AUC of FU adjusted for certain characteristics (BSA, UFT dose, performance status, complications) and found that the most significant factor was BSA (P = .0029). Because the dose of UFT administered in the pharmacokinetic study was not decided according to BSA, we examined the AUC of FU according to BSA. The result was that the distributions of the AUCs of FU were similar among patients in both countries in the same BSA range. Therefore, the AUCs of FU are thought to be comparable between Japanese and American patients. However, the reasons for the difference in diarrhea between the patients in the two countries having almost the same pharmacokinetic profile could not be identified, except for the possibility of racial influences.

5-MTHF is a metabolic product of LV, and 5-MTHF and LV are known to enhance the antitumor activity of FU. Our results also showed a slightly higher AUC and C_{max} of LV and 5-MTHF in the Japanese patients than in American patients. Meropol et al[30] has reported that there is no interaction between UFT and LV and that the plasma concentration of FU is unaffected by LV. This finding may suggest that the plasma concentration of FU is regulated by uracil, not LV, through inhibition of dihydropyrimidine dehydrogenase.

The results of the present study indicate that UFT/LV is equally active in Japanese and American patients. However, a difference in toxicity profile, especially diarrhea, was noted. Although the AUC and C_{max} of FU were found to be slightly higher in the Japanese patients than in the American patients, AUC-adjusted BSA appeared to be comparable between the countries. This oral regimen of UFT and LV was considered to have similar activity against metastatic colorectal cancer and to have acceptable toxicity in patients in both countries.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Squamous Cell Carcinoma In Situ at Oropharyngeal and Hypopharyngeal Mucosal Sites

Manabu Muto, M.D.[1]
Mari Nakane, B.S.[1]
Chikatoshi Katada, M.D.[1]
Yasushi Sano, M.D.[1]
Atsushi Ohtsu, M.D.[1]
Hiroyasu Esumi, M.D.[3]
Satoshi Ebihara, M.D.[2]
Shigeaki Yoshida, M.D.[1]

[1] Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan.

[2] Division of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan.

[3] National Cancer Center Research Institute East, Kashiwa, Japan.

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Address for reprints: Manabu Muto, M.D., Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan; Fax: (011) 81 4 7131 4724; E-mail: mmuto@east.ncc.go.jp

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BACKGROUND. Head and neck squamous cell carcinoma typically is diagnosed at an advanced stage, and the prognosis for patients with this type of malignancy is poor. Detection of these lesions at an earlier stage (e.g., as carcinoma in situ) would be of clear benefit to patients. However, it has been extremely difficult to detect carcinoma in situ at head and neck mucosal sites during routine endoscopy, even after numerous passes of the endoscope through the oral cavity and the pharynx.
METHODS. The current clinical investigation was performed during routine endoscopic screening or surveillance procedures. The authors used a novel optical technique, known as narrowband imaging (NBI) that allows noninvasive visualization of the microvascular structure of an organ's surface using reflected light.
RESULTS. Between April 2002 and August 2003, 34 consecutive superficial lesions were found in 18 patients. Multifocal carcinoma was found in 5 patients (28%). The median age of the patients examined was 59.5 years (range, 43–71 years), and 83% of all patients were male. All lesions exhibited a microvascular proliferation pattern on magnified NBI. Thirteen patients with a combined total of 29 lesions underwent endoscopic resection under general anesthesia. The pyriform sinus was the most frequent primary site (66%; 19 of 29 lesions). The median tumor diameter was 20 mm (range, 1.3–40 mm). Twenty-one lesions (72%) were histologically confirmed to be carcinoma in situ, and the remaining lesions showed evidence of microinvasion (0.05–1 mm) beneath the epithelium. Vascular invasion was observed in only one lesion. The median hospital stay was 10 days (range, 4–18 days). All patients were discharged without severe complications. After a median follow-up period of 8 months (range, 1–16 months), there were no cases of local disease recurrence.
CONCLUSION. The authors stress the importance of endoscopic detection of superficial carcinoma at oropharyngeal and hypopharyngeal mucosal sites. NBI is a promising and potentially powerful tool for identifying carcinomas at an earlier stage during routine endoscopic examination. ***Cancer* 2004;101:1375–81.**

KEYWORDS: carcinoma in situ, head and neck carcinoma, early detection, endoscopy, narrowband imaging system.

Annually, there are approximately 500,00 newly diagnosed cases of head and neck squamous cell carcinoma (HNSCC) worldwide. HNSCCs, and especially tumors of the hypopharynx, usually are diagnosed at an advanced stage and are associated with have a poor prognosis.[1–4] In addition, the extensive surgical resection that is required causes a loss of function with respect to swallowing and/or speaking and can also lead to cosmetic deformities. It is accepted that intraepithelial squamous dysplasia may progress to carcinoma in situ and eventually to invasive carcinoma. The ability to detect these lesions at an earlier stage, e.g., as carcinoma in situ, would be of clear

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benefit to patients. However, it is extremely difficult to detect in this region during routine endoscopic examination, even after many passes of the endoscope through the oral cavity and the pharynx.

Squamous dysplasia and carcinoma in situ in the esophagus can be made visible as Lugol-voiding lesions (LVLs) by lugol chromoendoscopy.[5] This method is now widely used in high-risk populations, such as heavy drinkers and heavy smokers, with the number of superficial malignancies detected increasing dramatically as a result. Endoscopic mucosal resection (EMR) is often used to treat patients with these lesions, as it is minimally invasive and yields a survival rate that is similar to the rates associated with other forms of surgery.[6] However, the Lugol staining method cannot be used in the head and neck region because it causes severe mucosal irritation, which leads to pain and discomfort and can even result in aspiration to the airway. If squamous dysplasia and carcinoma in situ in this region could be clinically recognized, EMR could be applied as a minimally invasive treatment modality.

Narrowband imaging (NBI) is a novel, noninvasive optical technique that uses reflected light to visualize the superficial structure of the organ surface.[7] Gono et al.[7] reported that magnified NBI clearly enhanced the epithelial microvascular pattern. Furthermore, Inoue et al.[8] and Kumagai et al.[9] reported that the morphologic changes in microvascular structure were useful in the diagnosis of superficial esophageal carcinomas. Although the importance of angiogenesis in the development of malignant disease is well recognized, the clinical significance of direct imaging of angiogenesis has not been elucidated. In the current study, we validated the use of the NBI system to detect superficial lesions at the head and neck mucosal sites.

MATERIALS AND METHODS

Principles of NBI

The NBI system is a new illumination method for medical endoscopy in which the spectral bandwidth of the filtered light is narrowed. The conventional medical videoendoscope system (EVIS 240; Olympus Co., Tokyo, Japan) uses three broadband optical filters that cover all wavelengths of the visible spectrum, which range from approximately 400 nm to 800 nm. In the NBI system, three narrowband filters are used, and the monochromic image signals corresponding to each filtered illumination are formed by a sequential illumination- and- conversion process carried out by the charge-coupled device. This generates a colored NBI view on the cathode-ray tube (CRT) monitor by assigning each monochromic image signal to a red, green, or blue (R/G/B) color channel in real time. In the current study, we assigned the F1 filter (center wavelength), 415 nm; full width at half-maximum [FWHM], 30 nm) to the B channel, the F2 filter (center wavelength, 445 nm; FWHM, 30 nm) to the G channel, and the F3 filter (center wavelength, 500 nm; FWHM, 30 nm) to the R channel as described previously.[7] Thin blood vessels such as capillaries on the mucosal surface can be seen most clearly at 415 nm, the wavelength corresponding to the hemoglobin absorption band.[7] In contrast, thick vessels located in the deep layer of the mucosa cannot be seen at all at 415 nm.[7] Using a set containing F1 and F2 filters, the microvasculature pattern can be seen in brown, and the contrast between normal mucosa and malignant lesions can be enhanced more clearly using this set of filters compared with any other.[7] These narrow-bandwidth filters make it possible to visualize malignant lesions, and especially lesions with fine microvasculature patterns.

Clinical Examination

The current clinical investigation was performed during routine endoscopic screening or surveillance procedures by a single endoscopist (M.M.) who was experienced in NBI endoscopy. All procedures were performed using a magnifying endoscope (GIF-Q240Z, Olympus Co.) in conjunction with the NBI system. Magnifying endoscopy possesses the capabilities of both standard video endoscopy and adjustable image magnification over a continuous range up to a magnification factor of 80. Before the endoscopic observation procedure was performed, each patient was sedated with 35 mg pethidine hydrochloride, and 20 mg scopolamine butylbromide was administered intravenously to patients who had any contraindications to pethidine.

Representative conventional endoscopic and corresponding NBI pictures of carcinoma in situ at the hypopharynx (Figs. 1–4) and at the oropharynx (Figs. 5–8) are shown.

At first, a nonmagnifying observation with NBI was performed to identify abnormal mucosal areas (Figs. 2, 6). If abnormal mucosal areas (e.g., well demarcated brownish lesions) were identified, photographs of the nonmagnified NBI view were taken. Subsequently, we observed the lesion and surrounding normal mucosa under magnification (Figs. 4, 8). If scattered brownish dots were observed within the lesion under the magnifying NBI, we diagnosed the lesion as being malignant, as has previously been reported for lesions in the esophagus.[8,9] We also attempted to detect these same lesions by conventional methods (Figs. 1, 3, 5, 8).

For patients with abnormal lesions, EMR was per-

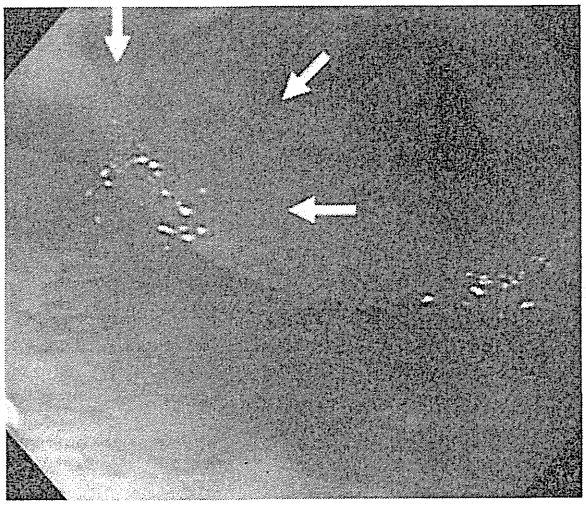

FIGURE 1. Squamous cell carcinoma in situ of the hypopharynx (tumor diameter, 12 mm). Conventional endoscopy shows slight reddish area in the left postcricoid area (arrows).

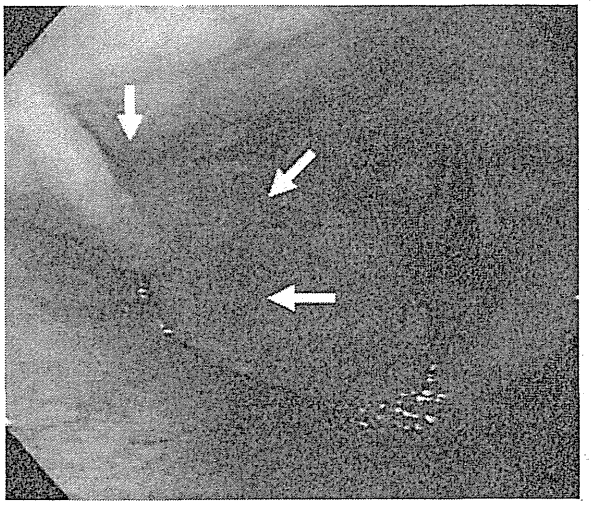

FIGURE 2. Squamous cell carcinoma in situ of the hypopharynx (tumor diameter, 12 mm). Narrowband imaging endoscopy shows a clearly demarcated brownish area in the left postcricoid area (arrows).

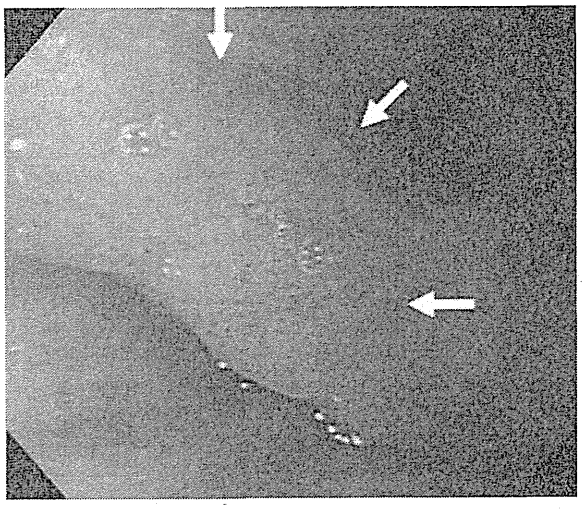

FIGURE 3. Squamous cell carcinoma in situ of the hypopharynx (tumor diameter, 12 mm). Magnified conventional endoscopy shows scattered reddish spots in the reddish area (arrows).

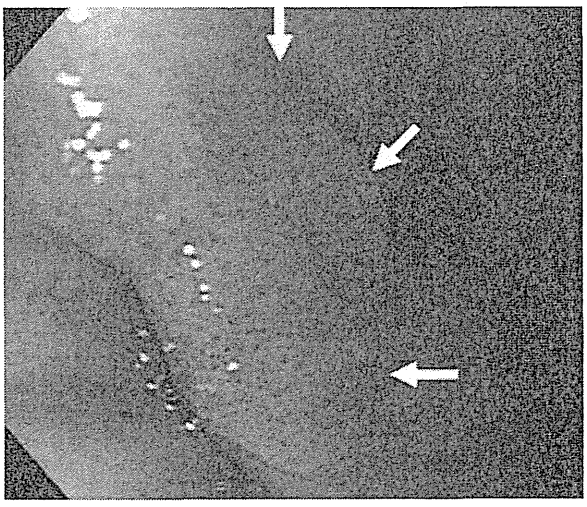

FIGURE 4. Squamous cell carcinoma in situ of the hypopharynx (tumor diameter, 12 mm). Magnified narrow band imaging endoscopy shows both a clearly demarcated brownish area and scattered, clearly defined brown spots (arrows). These spots represent a microvascular proliferation pattern.

formed under general anesthesia. Lesions were removed using a transparent plastic soft cap (EMR procedure with a cap-fitted panendoscope[10] by inserting a needle next to the lesion and injecting an adequate volume of saline containing diluted epinephrine (0.02 mg/mL) beneath the epithelium to lift it above the surrounding mucosa. The lesion was removed using a snaring method under the conditions of the Autocut-120 (Effect 2 or 3)/Endo-Cut, mode of the ICC 200 electrosurgical generator (ERBE, Tubingen, Germany). Resected specimens were extended on boards with pins and fixed in 10% formalin for 24 hours. Diagnostic accuracy was estimated on the basis of the histologic results yielded by biopsy specimens. Written informed consent was obtained from all patients before examination and EMR.

RESULTS

Between April 2002 and August 2003, we identified a total of 34 consecutive superficial lesions in 18 pa-

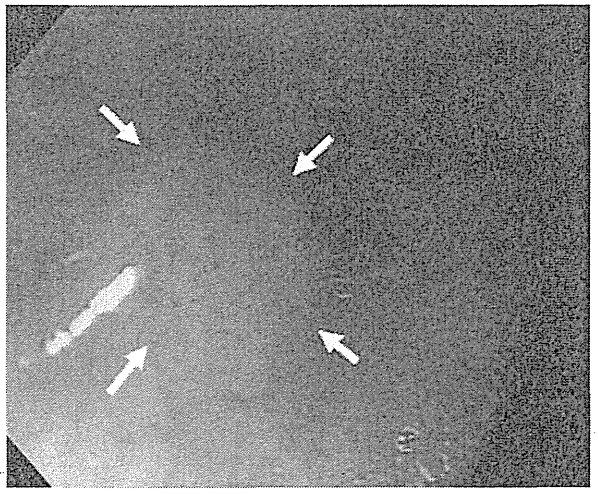

FIGURE 5. Squamous cell carcinoma in situ in the oropharynx (tumor diameter, 3 mm). Conventional endoscopy.

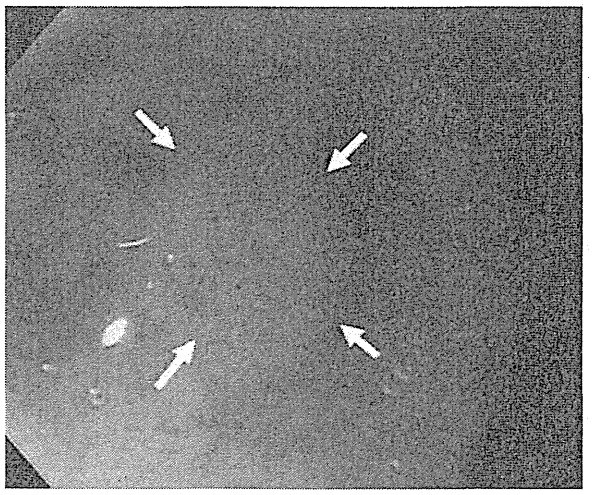

FIGURE 6. Squamous cell carcinoma in situ of the oropharynx (tumor diameter, 3 mm). Magnified conventional endoscopy.

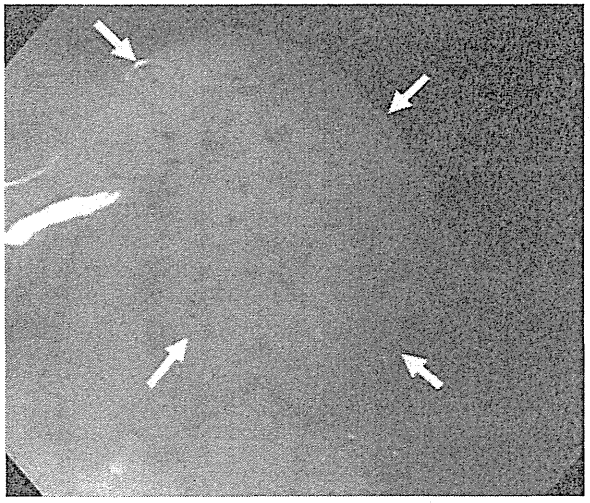

FIGURE 7. Squamous cell carcinoma in situ of the oropharynx (tumor diameter, 3 mm). Narrowband imaging endoscopy.

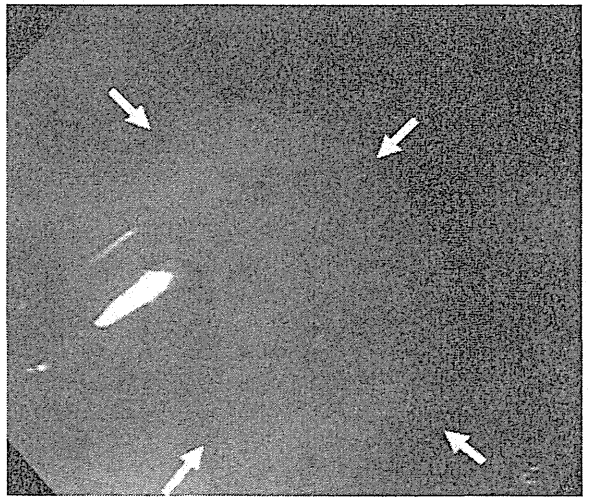

FIGURE 8. Squamous cell carcinoma in situ of the oropharynx (tumor diameter, 3 mm). Magnified narrowband imaging endoscopy.

tients (Table 1). The median age of the patients was 59.5 years (range, 43–71 years), and 83% of all patients were male. On nonmagnifying NBI observation, all of the lesions were recognized as well demarcated brownish areas. In addition, all of the lesions exhibited scattered brown dots within these areas on magnified NBI observation. Therefore, all were suspected to be malignant lesions. In contrast, by conventional observation, only four lesions and one lesion, respectively, were found to contain well demarcated brownish areas and scattered brown dots. Thus, it was very difficult to identify malignant lesions by conventional observation. To obtain histologic confirmation of these lesions, we obtained biopsy specimens from all 18 patients. All of these lesions were histologically diagnosed as squamous cell carcinomas.

EMR was performed in 13 patients (with a combined total of 29 lesions). Of the remaining five patients, one was treated with radiotherapy because the lesion was too large to be removed surgically, one underwent complete surgical resection of the squamous cell carcinoma together with resection of another advanced malignancy of the tongue, two were followed without treatment because they had ad-

TABLE 1
Clinicopathologic Features of Patients with Superficial Head and Neck Carcinoma

Patient no.	Age (yrs)	Gender	Multifocal superficial lesions	Treatment procedure	Total no. of lesions	Hospital stay after EMR (days)	Local disease recurrence after EMR	Time to development of new lesion after EMR (mos)	Follow-up period (mos)	Multiple LVLs	EC (no.)	Treatment for EC
1	52	M	Yes	EMR	8	10	No	15	16	Yes	Yes (1)	CRT
2	64	M	No	EMR	1	8	No	—	12	Yes	Yes (3)	EMR
3	50	M	No	EMR	1	8	No	—	12	Yes	Yes (3)	EMR and CRT
4	47	F	Yes	EMR	3	15	No	14	14	Yes	Yes (5)	EMR
5	52	M	No	EMR	1	9	No	—	11	Yes	Yes (4)	EMR
6	53	M	No	EMR	1	12	No	—	6	Yes	Yes (4)	EMR
7	65	M	Yes	EMR	2	8	No	4	9	Yes	Yes (1)	EMR
8	43	M	No	EMR	1	4	No	—	8	Yes	Yes (5)	EMR
9	64	M	Yes	EMR	6	17	No	—	6	Yes	Yes (3)	EMR
10	67	M	No	EMR	1	18	No	—	3	Yes	No	—
11	65	M	Yes	EMR	2	10	No	—	2	Yes	Yes (1)	EMR
12	60	M	No	EMR	1	8	No	—	1.5	Yes	Yes (3)	EMR
13	58	M	No	EMR	1	15	No	—	1	Yes	No	—
14	44	F	No	F/U	1	NE	NE	NE	NE	Yes	Yes (2)	CRT
15	59	M	No	Radiation	1	NE	NE	NE	NE	Yes	Yes (2)	EMR
16	71	F	No	SLR	1	NE	NE	NE	NE	Yes	No	—
17	60	M	No	F/U	1	NE	NE	NE	NE	Yes	Yes (1)	CRT
18	62	M	No	F/U	1	NE	NE	NE	NE	Yes	Yes (1)	EMR

EMR: endoscopic mucosal resection; F/U: follow-up; SLR: surgical local resection; EC: esophageal carcinoma; CRT: chemoradiotherapy; NE: not evaluable; M: male; F: female; LVL: Lugol-voiding lesion.

vanced esophageal carcinoma, and one was followed without treatment because of unresectable oropharyngeal malignancy.

All 13 patients who underwent EMR were hospitalized. The median hospital stay was 10 days (range, 4–18 days). All were discharged without severe complications. The median follow-up period was 8 months (range, 1–16 months), and no cases of local disease recurrence were detected after EMR. Three patients (23%) developed new superficial malignancies in the hypopharynx or oropharynx, all of which were removed by subsequent EMR procedures.

The histologic characteristics of the 29 lesions treated with EMR are summarized in Table 2. The pyriform sinus was the most common primary site (66% [19 of 29]). The median tumor diameter was 20 mm (range, 1.3–40 mm). Twenty-one lesions (72%) were histologically confirmed to be carcinoma in situ, and the remainder exhibited microinvasion beneath the epithelium. Vascular invasion was observed in only one lesion.

Magnified NBI clearly revealed scattered brown dots within all malignant lesions. These dots were histologically confirmed to be dilated, with increased microvasculature in the epithelium, on immunohistochemical staining with antihuman monoclonal CD-31 antibody (DakoCytomation, Kyoto, Japan) (Figs. 9, 10). This microvascular proliferation (MVP) pattern was observed in all lesions by NBI (Figs. 4, 8), whereas the MVP pattern was rarely detected by conventional observation, even with magnification (Figs. 3, 7).

In the current study study, all patients had multiple LVLs in the background esophageal mucosa. Furthermore, 15 patients (83%) had esophageal carcinomas, and 10 of these malignancies (67%) were multifocal. In addition, multifocal superficial lesions at oropharyngeal and hypopharyngeal mucosal sites were identified in 5 patients (28%).

DISCUSSION

Our results suggest that carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites can be clinically recognized using magnified NBI endoscopy. Thus, the NBI technique could significantly improve the efficacy of screening for and surveillance of lesions of the head and neck region, and especially lesions at oropharyngeal and hypopharyngeal mucosal sites.

In addition, the development of synchronous and metachronous SCC at head and neck mucosal sites is a critical problem, because this event is correlated with poor disease control and poor survival rates.[11] Although this is well recognized as the *field cancerization* phenomenon,[12] which typically is associated with repeated exposure to carcinogens such as alcohol and cigarette smoke, no effective screening or follow-up strategies have been developed. We previously reported that multiple occurrences of LVL (multiple LVLs) were closely associated with the field canceriza-

TABLE 2
Characteristics of Lesions Treated with EMR

Characteristic	No. of lesions
Primary site	
Hypopharynx	
Right pyriform sinus	11
Left pyriform sinus	8
Posterior pharyngeal wall	2
Right postcricoid area	5
Left postcricoid area	1
Oropharynx	
Uvula	2
Lateral wall	0
Microvascular proliferation pattern on NBI	
Present	29
Absent	0
Macroscopic appearance of lesions	
Elevated	3
Flat	26
Depressed	0
Tumor size (mm)	
≤ 5	9
> 5 and ≤ 10	7
> 10 and ≤ 20	7
> 20 and ≤ 30	4
> 30 and ≤ 40	2
Histology	
Carcinoma in situ	21
Microinvasion (mm)	8
≤ 0.5	5
≥ 0.5 and ≤ 1	2
> 1	1
Vascular invasion	
Present	1
Absent	28

EMR: endoscopic mucosal resection.

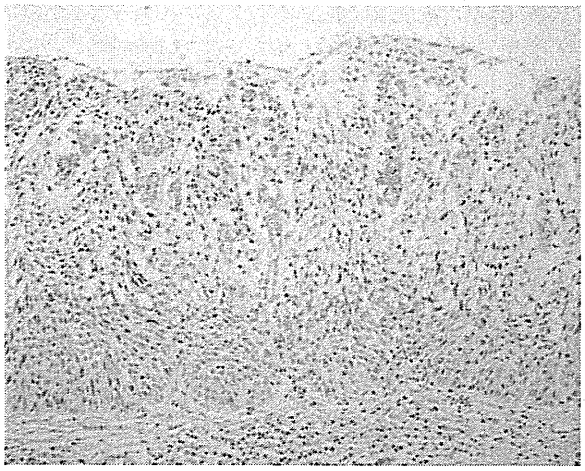

FIGURE 9. Squamous cell carcinoma in situ of the hypopharynx (tumor diameter, 12 mm). Hematoxylin and eosin staining. Original magnification ×100.

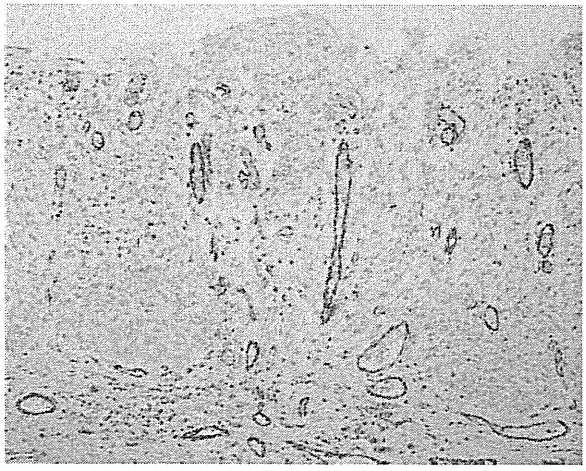

FIGURE 10. Squamous cell carcinoma in situ of the hypopharynx (tumor diameter, 12 mm). Microvascular proliferation identified by CD-31 immunohistochemical staining. Original magnification ×100.

tion phenomenon.[5,13,14] Among patients with HNSCC, multiple LVLs were significantly associated with synchronous and metachronous multiple esophageal SCCs. In the current series, all patients had multiple LVLs in the background esophageal mucosa. Furthermore, 67% and 28% of patients developed multifocal carcinoma in the esophagus and in the oropharyngeal/hypopharyngeal mucosa, respectively. The theory of field cancerization suggests that multiple LVLs could represent a powerful biomarker for multiple malignancies not only in the esophagus, but also at head and neck mucosal sites. Therefore, it would be of great interest to conduct a study involving prospective screening and follow-up to detect synchronous and metachronous carcinomas at head and neck mucosal sites among patients with or without multiple LVLs using NBI endoscopy.

Clinically, early detection and prevention are among the most important strategies for improving survival and quality of life for patients with malignant disease. Backman et al.[15] showed that light-scattering spectroscopy had the potential to detect premalignant epithelial lesions and preinvasive malignancies by noninvasive means. This technique yields quantitative information on nuclear morphology in the epithelial layers. In contrast, the NBI technique enhances the information available on microvascular structure in epithelial layers.[7] Therefore, we can easily identify the MVP pattern, which is defined by the presence of scattered brown dots, using NBI, even in patients with squamous cell carcinoma in situ. This finding indi-