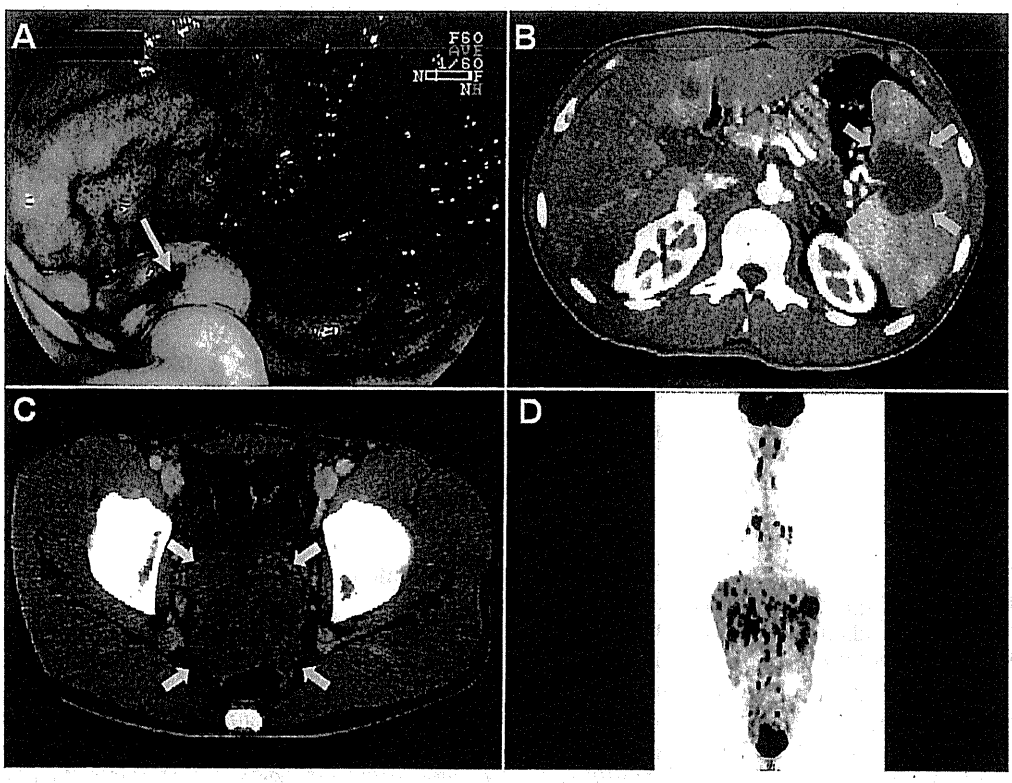

Figure 1. Endoscopic and radiological findings on admission. Endoscopy showed oozing bleeding from gastric varices (A, arrow shows bleeding point). Compression of the splenic vein by the splenic hilar tumor appeared to cause the gastric varices (B, arrows). A well-enhanced, bulky and lobulated tumor located on the pelvic floor was thought to be the primary lesion (C, arrows). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography revealed intense FDG uptake in the same tumors detected using computed tomography (D, a primary lesion, a splenic hilar tumor and multiple liver, lung and lymph node lesions).

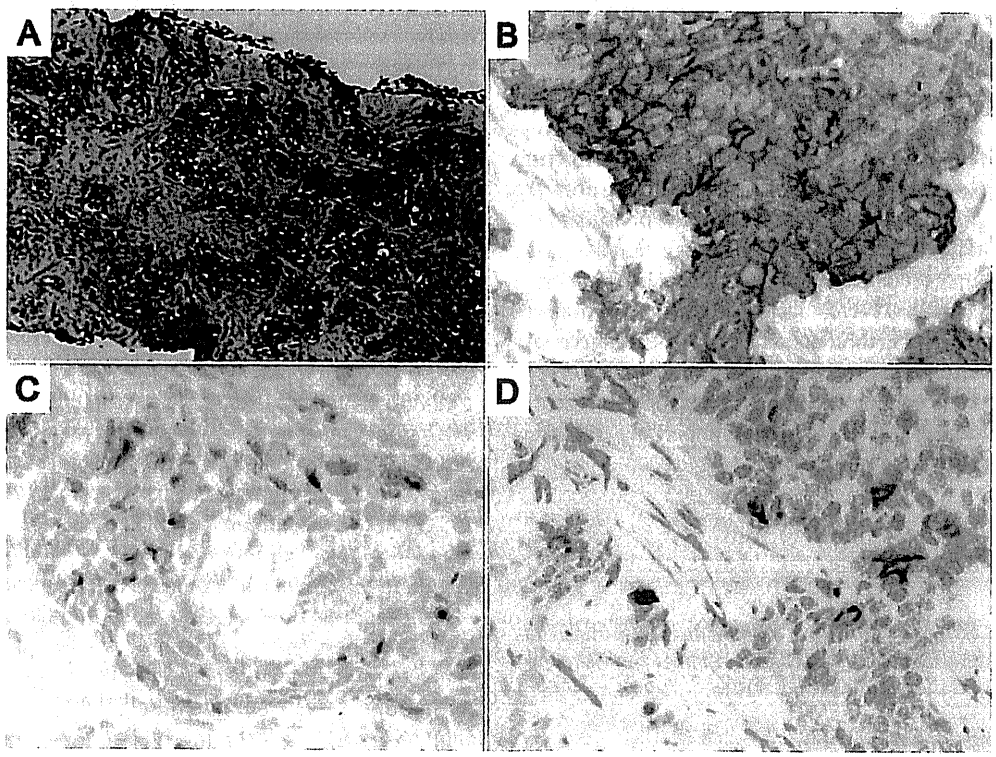

Figure 2. Representative pathological features of a needle biopsy specimen from the liver tumor. Hematoxylin and eosin staining showed poorly differentiated tumor cells with variable size and shape, composed of nests of small round cells and surrounded by a prominent desmoplastic stroma (A, magnification, x100). Immunohistochemical staining was positive for (B) cytokeratin (magnification, x400), (C) desmin (magnification, x400) and (D) Wilms' tumor 1 protein (magnification, x400).

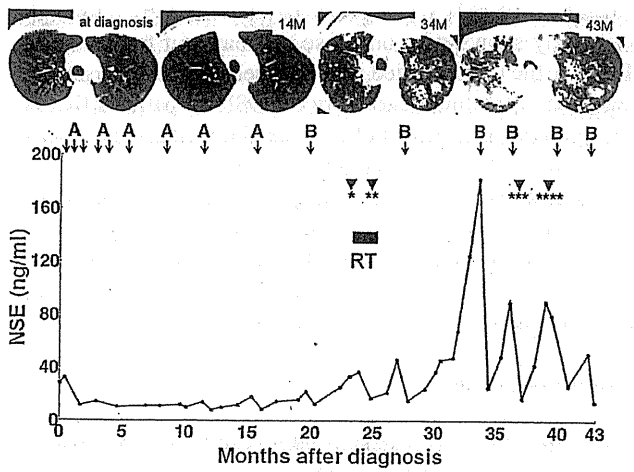

Figure 3. Clinical course of this case. Serum NSE level correlated well with clinical response. The patient received (A) nine courses of a modified P6 regimen and (B) six courses of a modified PAVEP regimen. Obstructive jaundice caused by portal lymphadenopathy was treated successfully by repeated endoscopic biliary drainage and radiation therapy (RT) to the hepatic portal region using 42.5 Gy, at 1.8 Gy per fraction. Massive hematemesis caused by active bleeding from the varicose vein was treated successfully by endoscopic hemostasis. The patient succumbed to acute pulmonary failure caused by progressive pulmonary metastases 43 months following diagnosis. Time-series CT images of pulmonary metastases are shown in parallel in the upper column (M, months after diagnosis). *Endoscopic biliary drainage using a plastic stent; **endoscopic biliary drainage using a metal stent; ***endoscopic hemostasis using metal clips for the active bleeding from a varicose vein; ****the metal stent obstruction caused by tumor ingrowth was relieved by inserting a plastic stent into the prior metal stent. NSE, neuron-specific enolase.

the hepatic portal region). ^{18}F-fluorodeoxyglucose positron emission tomography showed multiple accumulation of a glucose analog in the same lesions detected using CT (Fig. 1D).

A needle biopsy specimen from the liver tumor revealed the presence of a poorly differentiated tumor with a variable size and shape, composed of nests of small round cells surrounded by a prominent desmoplastic stroma (Fig. 2A). Immunohistochemically, tumor cells coexpressed an epithelial marker (cytokeratin, Fig. 2B), a mesenchymal marker (desmin, Fig. 2C) and the Wilms' tumor 1 protein (Fig. 2D). Chromogranin, cluster of differentiation antigen (CD) 99 and CD56 were negative. From these findings, the patient was provided with a definite diagnosis of pelvic cavity-origin DSRCT with multiple-organ metastases (4,5).

The clinical course of this case is shown in Fig. 3. The patient was initially treated with multiagent chemotherapy using cyclophosphamide, pirarubicin, vincristine, ifosfamide and etoposide, according to the Ewing's sarcoma protocol, which is a modified protocol of the P6 regimen using pirarubicin instead of doxorubicin (modified P6 regimen) (2,6). During each course of this chemotherapy, the patient suffered from severe nausea and vomiting. The patient required frequent blood transfusions and continuous use of granulocyte colony-stimulating factor due to severe bone marrow suppression. The multiple pulmonary metastases were almost eradicated following four courses of the modified P6 regimen and the patient reached 15 months of progression-free survival after the application of this modified P6 regimen (Fig. 3). After the nine courses of treatment, second-line chemotherapy based on the PAVEP regimen (doxorubicin, cyclophosphamide, etoposide and cisplatin) (7) was introduced due to disease progression. To reduce adverse events, we modified the PAVEP regimen by using pirarubicin instead of doxorubicin and shortening the period of the regimen from five to two days (modified PAVEP regimen). The P6, modified P6, PAVEP and modified PAVEP regimens are shown in Table I.

Obstructive jaundice caused by portal lymphadenopathy developed 23 months following diagnosis. Endoscopic biliary drainage using a plastic stent was successfully performed. However, stent obstruction occurred two months after the initial placement of the plastic stent. Subsequently, we removed the stent and inserted a metal stent, which was followed by irradiation of the hepatic portal region using a total dose of 42.5 Gy, at 1.8 Gy per fraction. The patient had massive hematemesis 37 months following diagnosis caused by the active bleeding from a known varicose vein and endoscopic hemostasis using

Table I. Chemotherapy regimens reported previously and used in this case.

	Dose	Day
P6 (6)		
Courses 1, 2, 3 and 6		
Cyclophosphamide	2.1 g/m^2	1-2
Doxorubicin	25 mg/m^2	1-3
Vincristine	0.67 mg/m^2	1-3
Courses 4, 5 and 7		
Ifosfamide	1.8 g/m^2	1-5
Etoposide	100 mg/m^2	1-5
PAVEP (7)		
Doxorubicin	40 mg/m^2	1
Cyclophosphamide	300 mg/m^2	1-3
Etoposide	75 mg/m^2	1-3
Cisplatin	100 mg/m^2	4
Modified P6		
Courses 1, 3, 5 and 7		
Cyclophosphamide	2 g/m^2	1-2
Pirarubicin	20 mg/m^2	1-3
Vincristine	2 mg/m^2	1
Courses 2, 4 and 6		
Ifosfamide	2.5 g/m^2	1-5
Etoposide	100 mg/m^2	1-5
Modified PAVEP		
Pirarubicin	40 mg/m^2	2
Cyclophosphamide	450 mg/m^2	1-2
Etoposide	110 mg/m^2	1-2
Cisplatin	100 mg/m^2	1

Courses started after confirmation that the neutrophil count reached 500/μl and that the platelet count was >10,000/μl.

metal clips was obtained successfully. Furthermore, metal stent obstruction caused by tumor ingrowth occurred 39 months following diagnosis, which was relieved by inserting a plastic stent into the metal stent placed previously. After 15 courses of chemotherapy, radiation therapy and four instances of endoscopic therapy (Fig. 3), the patient experienced sudden respiratory arrest caused by bronchial obstruction by the parabronchial multiple lung metastatic lesions. Despite intensive care, including intubation and one course of chemotherapy, the patient succumbed to the disease 43 months after diagnosis.

Discussion

DSRCT was first described in 1989 by Gerald and Rosai (8). DSRCT is a rare aggressive tumor with few long-term survivors and the prognosis of patients with DSRCT has not improved substantially since the first description of the disease. The rarity of this tumor has prevented the development of standard therapy for DSRCT. DSRCT has been reported as being associated with a characteristic reciprocal translocation [t(11; 22) (p13; q12)], which fuses the Ewing's sarcoma gene on chromosome 22 to the Wilms' tumor gene on chromosome 11 (9). This translocation is reflected by the immunohistological expression of the Wilms' tumor 1 protein in the tumor (10). The neuron-specific enolase (NSE) and CA125 proteins are tumor markers that are elevated in DSRCT patients and correlate specifically with response to treatment (11). The serum NSE levels in our case correlated well with clinical response, as shown in Fig. 3. The prolonged (15 months) progression-free survival obtained following multiagent chemotherapy suggests that DSRCT is a chemosensitive disease, as mentioned in previous studies (1,12).

Efforts have been made to establish treatments aimed at controlling this disease. One of them was the combination of aggressive surgery (to resect visible disease), radiation therapy to the tumor bed and myeloablative multiagent chemotherapy (6). A recent report from the Memorial Sloan-Kettering Cancer Center experience (2) showed that overall survival in 66 patients was 44% at three years and 15% at five years using a combination of the P6 regimen, surgical debulking and radiotherapy to a dose of 30 Gy. However, more than half of these patients had no distant metastasis. Currently, there is no standard therapy for patients with DSRCT, particularly for inoperable/metastatic DSRCT cases, and there are few reports of metastatic DSRCT treatment (13). To the best of our knowledge, this is the first case of metastatic DSRCT in a patient who lived for more than three years without surgical resection (14). Multi-institutional randomized control trials for DSRCT are not available due to the rarity of the disease. Another attempt at developing treatments for this disease was the use of a novel molecularly targeted therapy and a new chemical agent (15). We examined the expression of c-kit, androgen receptor, CD20 and epidermal growth factor receptor using a biopsy sample (16,17). However, we found that none of the markers were expressed in tumor cells; therefore, we could not use any molecularly targeted agent in this case.

In this study, we used pirarubicin instead of doxorubicin in the P6 regimen administered to this patient, as pirarubicin may be relatively superior to doxorubicin regarding side effects (18). Moreover, the use of pirarubicin in a multiagent regimen for DSRCT was previously reported (6,7). Although our study shows only one case of treatment for metastatic DSRCT, the two modified regimens selected for our case may represent a treatment modality for DSRCT patients that has the potential advantages of decreased toxicity and improved completion rate of the chemotherapy regimen.

In conclusion, DSRCT is an aggressive but chemosensitive disease and continuous chemotherapy using an appropriate regimen with possible supportive care is essential for the long-term survival of these patients. This case report may present a treatment option for this rare disease.

Acknowledgements

We are grateful to the patient and his family for their permission to report our experience with his case.

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Impact of Neoadjuvant Chemotherapy on Physical Fitness, Physical Activity, and Health-related Quality of Life of Patients With Resectable Esophageal Cancer

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Objective: Neoadjuvant chemotherapy (NAC) followed by radical surgery is the standard treatment for patients with resectable esophageal squamous cell carcinoma (ESCC) in Japan. However, some adverse events associated with NAC may result in a decrease in physical fitness that may influence the patient's ability to tolerate surgery. The purpose of this study was to evaluate the impact of NAC on physical fitness, physical activity, and health-related quality of life (HRQOL) of patients with ESCC.

Methods: In this prospective study, we investigated 27 consecutive patients with newly diagnosed resectable ESCC who were scheduled to receive NAC followed by surgery between January 2009 and November 2010. Primary endpoints were change from baseline in physical fitness (knee extensor muscle strength and 6-min walking distance) and physical activity after NAC. A secondary endpoint was change from baseline in HRQOL.

Results: Physical fitness and physical activity level after NAC did not differ significantly from those before NAC. With regard to HRQOL, only social functioning was significantly different ($P=0.04$). The change in physical activity demonstrated a significant correlation with the change in 6-minute walking distance ($r=0.45$, $P=0.02$).

Conclusions: NAC had no impact on physical fitness and physical activity in patients with ESCC. This result indicated that there was no need for a physiotherapy intervention during NAC to prevent a decline in these parameters.

Key Words: esophageal cancer, HRQOL, neoadjuvant chemotherapy, physical activity, physical fitness

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Esophageal cancer was the eighth most common malignancy (482,000 cases, 3.8% of all cancers) and the sixth leading cause of cancer death (406,000 deaths, 5.4% of all cancers) worldwide in 2008.[1] Despite optimal treatment, median survival for advanced disease remains <1 year. Even in patients with resectable disease, the prognosis is relatively poor after surgery alone.[2–4] This fact has prompted many investigators to explore perioperative systemic treatment, such as chemotherapy or chemoradiotherapy, to improve survival. In Japan, on the basis of the results of several studies, such as Japan Clinical Oncology Group 9204 and Japan Clinical Oncology Group 9907, neoadjuvant chemotherapy (NAC) with cisplatin combined with 5-fluorouracil followed by radical surgery has become the standard treatment strategy for resectable esophageal squamous cell carcinoma (ESCC).[5,6]

Although NAC is a well-established treatment for improving the outcomes of surgery, several side effects may result in the deterioration of physical fitness, physical activity, and health-related quality of life (HRQOL). Recently, several studies reported the impact of neoadjuvant treatment (chemotherapy or chemoradiotherapy) on HRQOL.[7–9] However, there are no reports on the impact of NAC on physical fitness or physical activity. It is important to clarify whether these parameters will be decreased by NAC, because the compromise of physical fitness by NAC may negatively influence the tolerability and outcome of surgery. In addition, the results of this study will be useful to determine whether a physiotherapy intervention is necessary during the neoadjuvant treatment period to improve these parameters.

The objectives of this study were to evaluate the impact of NAC on physical fitness, physical activity, and HRQOL in patients with ESCC and to determine whether physiotherapy is needed during the NAC period.

MATERIALS AND METHODS

Study Design and Subjects

This was a single-center, prospective study conducted to evaluate the impact of NAC on the physical fitness, physical activity, and HRQOL of patients with resectable ESCC. The Institutional Review Board of Kyoto University Graduate School of Medicine approved the protocol and consent form for this study, and written informed consent was obtained from all patients. Between January 2009 and November 2010, patients with newly diagnosed ESCC who were scheduled to receive NAC followed by surgery were asked to participate in this study. All the patients who were scheduled to receive NAC followed by surgery were eligible. Patients with gait disturbances or cognitive impairment were excluded. Preoperative chemotherapy consisted of 2 cycles of cisplatin (80 mg/m^2, intravenously) on day 1 and 5-fluorouracil (800 mg/m^2/d in a continuous infusion) on days 1 through 5 at 3-week intervals. Primary outcomes were physical fitness (knee extensor muscle strength and 3-min walking distance) and physical activity. The secondary outcome was HRQOL. We assessed these outcomes before the initiation of NAC (pre-NAC) and after the completion of NAC (post-NAC).

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The authors declare no conflicts of interest.

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Demographic and Treatment Information

Information regarding age, sex, weight, clinical stage, histologic tumor type, and side effects was obtained from electronic medical records. Side effects were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. The National Cancer Institute Common Terminology Criteria for Adverse Events measure toxicities as grades 1 through 5 (1 is mild, 2 is moderate, 3 is severe, 4 is life threatening or disabling, and 5 is death associated with the adverse event).

Physical Fitness

To assess physical fitness, we tested the knee extensor muscle strength and 6-minute walking distance. Knee extensor muscle strength was assessed with an isometric knee extensor muscle strength machine (IsoForce GT-330, OG GIKEN, Japan). The subject was in the sitting position, and the hip and knee were kept at 90-degree angle. The maximal isometric strength was measured after adequate premeasurement trials. The 6-minute walking distance was measured with the 6-minute walk test, as described by the American Thoracic Society.[10] Subjects walked as far and as fast as they could for 6 minutes. (Subjects were allowed to rest if and as necessary during the 6-min period.) These tests were conducted by physiotherapists who had been trained in the proper techniques for conducting them.

Physical Activity

Physical activity status was assessed using the last 7-day short version of the International Physical Activity Questionnaire (IPAQ) Japanese version.[11,12] This measure assessed total vigorous intensity physical activity, total moderate intensity physical activity, total time walking, and time spent sitting during the last 7 days. Each activity type and intensity score is provided a metabolic equivalent (MET) value according to the published protocol (eg, MET for walking = 3.3, cycling = 6.0, moderate intensity = 4.0, vigorous intensity leisure = 8.0) (Craig, IPAQ. At a glance: IPAQ scoring protocol, http://www.ipaq.ki.se/scoring.htm, accessed March 20, 2006). According to the published IPAQ scoring protocol, we calculated the average daily physical activity (METs min/d).

Health-related Quality of Life

HRQOL was measured with the European Organization for the Research and Treatment of Cancer Quality of Life (QOL) Core Questionnaire with 30 items.[13] This QOL scale includes a global health status/QOL scale, 5 functional scales (physical, role, emotional, cognitive, and social functioning), and symptom scales (fatigue, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems). Calculation of scores was carried out according to the European Organization for the Research and Treatment of Cancer QOL Core Questionnaire with 30 items manual. A difference of ≥ 10 points in each scale indicates a clinically important change.[14]

Sample Size Calculation and Statistical Analysis

Sample size calculation was based on the difference in the 6-minute walk test; primary outcome in this study. As the walking distance of 54 m (SD = 93) was thought to be clinically an important difference,[15–18] the estimated sample sizes required to achieve a power of the test of 80% and a 2-sided level of significance of 5% were calculated as 27 patients.

Demographic and treatment variables were described using means and SD, medians and ranges, and percentages, where appropriate. All variables were tested for distribution normality using the Shapiro-Wilks normality test. Differences over the course of NAC (pretreatment to posttreatment) were analyzed using paired-sample *t*-test for continuous variables with normal distribution (weight, knee extensor muscle strength, and 6-min walking distance) and the Wilcoxon signed-rank test for non-normally distributed variables (IPAQ score and HRQOL scores). Spearman rank correlation coefficient was used to evaluate the relationship between changes in physical activity and changes in physical fitness. All statistical analyses were performed with the R statistical package (www.r-project.org). All hypothesis testing was 2-tailed, and P values < 0.05 were considered to indicate statistical significance.

RESULTS

During the study period, 33 patients with ESCC underwent NAC before surgery. Among them, 6 were excluded because of gait disturbances (n = 2), cognitive impairment (n = 1), and declined participation (n = 3), so the remaining 27 patients were properly registered and underwent NAC. Patient demographic and treatment data are presented in Table 1. The mean age was 63 years, and 81% were men. The baseline clinical stage (UICC-TNM stage 6th edition) at enrollment was IIA in 11 (41%) patients, IIB in 10 (37%) patients, III in 5 (18%) patients, and IVA in 1 (4%) patient. The histologic type was squamous cell carcinoma in all patients. The occurrence of side effects was as follows: grade 1 in 23 (85%) patients, grade 2 in 16 (59%) patients, grade 3 in 3 (11%) patients, and grade 4 in 1 (4%) patient. The grade 3 chemotherapy-related toxicities were mucositis, abdominal pain, and thrombocytopenia. The grade 4 chemotherapy-related toxicity was hyponatremia. Most patients underwent 2 cycles of preoperative chemotherapy, although 5 (19%) patients underwent only 1 cycle because of severe adverse events (n = 2) and progression of disease (n = 3).

Table 2 shows changes in weight, physical fitness data, and physical activity over the course of NAC. Post-NAC variables did not differ significantly from pre-NAC variables. With regard to the global health status/QOL scale, functional scales, and symptom scales, there was a statistically significant difference only in terms of social functioning ($P = 0.04$; Table 3).

Results of the correlational analysis are presented in Figures 1A, B. The change in physical activity demonstrated a significant correlation with the change in 6-minute walking distance ($r = 0.45$, $P = 0.02$), but not with the change in knee extensor muscle strength ($r = -0.01$, $P = 0.95$).

DISCUSSION

This is the first report regarding the impact of NAC on physical fitness and physical activity. Results of this prospective study suggested that NAC had no impact on physical fitness, physical activity, and HRQOL in patients with ESCC. We hypothesized that physical activity would decrease because of adverse events, leading to a deterioration in physical fitness. Several studies have reported that treatment (surgery and/or chemotherapy and/or radiation) had a significant negative effect on physical activity.[19,20] In our study, however, physical fitness and physical activity levels did not decrease over the course of NAC. In addition, the change in physical activity demonstrated a significant positive correlation with the change in 6-minute walking distance. These results indicated that patients who maintained their pretreatment physical activity levels could maintain physical fitness, especially the 6-minute walking distance. Although most patients in this study experienced some kind of adverse event,

TABLE 1. Characteristics of Subjects

	N=27 (%)
Age (mean±SD)	63.4±6.8
Sex	
Male	22 (81%)
Female	5 (19%)
Clinical stage	
IIA	11 (48%)
IIB	10 (37%)
III	5 (18%)
IVA	1 (4%)
Histologic tumor type	
Adenocarcinoma	0 (0%)
Squamous cell carcinoma	27 (100%)
Side effects	
Grade 1	23 (85%)
Grade 2	16 (59%)
Grade 3	3 (11%)
Grade 4	1 (4%)
Grade 5	0 (0%)

TABLE 3. Changes in EORTC QLQ-C30 Over the Course of NAC Treatment

	Pre-NAC	Post-NAC	*P*
Global health status (QOL score)	66.7 (16.7-100)	66.7 (16.7-91.7)	NS
Functional scales			
Physical	93.3 (66.7-100)	93.3 (60-100)	NS
Role	100 (33.3-100)	100 (33.3-100)	NS
Emotional	75 (41.7-100)	83.3 (50-100)	NS
Cognitive	83.3 (50-100)	83.3 (33.3-100)	NS
Social	100 (33.3-100)	83.3 (0-100)	0.04
Symptom scales			
Fatigue	22.2 (0-55.6)	22.2 (0-66.7)	NS
Nausea and vomiting	0 (0-33.3)	0 (0-66.7)	NS
Pain	0 (0-50)	0 (0-33.3)	NS
Dyspnea	0 (0-66.7)	0 (0-33.3)	NS
Insomnia	0 (0-66.7)	0 (0-66.7)	NS
Appetite loss	0 (0-66.7)	0 (0-100)	NS
Constipation	0 (0-100)	0 (0-100)	NS
Diarrhea	0 (0-33.3)	0 (0-33.3)	NS
Financial difficulties	0 (0-100)	0 (0-100)	NS

Values expressed as median (range).
EORTC QLQ-C30 indicates European Organization for the Research and Treatment of Cancer Quality of Life Core Questionnaire with 30 items, NAC, neoadjuvant chemotherapy; NS, not significant; QOL, quality of life.

the severity of these adverse events was relatively mild. This seemed to be one of the reasons that most patients could maintain their physical activity levels. Similarly, HRQOL scores did not deteriorate significantly over the course of NAC, except for social functioning. Our findings are similar to previous work by Safieddine et al, who reported that the impact of NAC on HRQOL in patients with operable esophageal cancer was transient because HRQOL scores returned to baseline levels before surgical intervention.[7]

It was important to understand the impact of NAC on physical fitness, physical activity, and HRQOL in patients with ESCC to determine the need for a physiotherapy intervention to improve these parameters during NAC. The results of the present study indicated that there was no need for a physiotherapy intervention during NAC. However, Nagamatsu et al reported that esophagectomy can be safely performed in patients with a Vo^2 max/m^2 of at least 800 mL/m^2.[21] Thus, physiotherapy may be important before surgery to reduce the risk of postoperative cardiopulmonary complications. Further studies are needed to examine the role of physiotherapy in the treatment of ESCC comprehensively.

This study has some limitations. First, our study was conducted with small sample size, which might not have had enough power to detect significant differences in outcomes. It was possible that each outcome might reach statistical significance with more patients. However, even so, they might not be clinically significant; such as 1 kg weight loss, minimal difference in knee strength, or 2% difference in walk distance. Although only the 17% difference in IPAQ might be a clinically significant difference with more patients, the conclusion of this study might not be changed, because IPAQ was the secondary outcome. In addition, the small sample size precluded subgroup analyses stratified by the demographic and treatment characteristics of the patients. Second, we evaluated the impact of chemotherapy alone as a neoadjuvant treatment, because NAC followed by surgery is the standard treatment for the patients with resectable disease in Japan. However, the standard neoadjuvant treatment for the esophageal cancer in Western countries, such as in United States or in Europe, is chemotherapy with more strong combination regimen or chemoradiotherapy. Although it might be possible that inclusion of patients who received neoadjuvant chemoradiotherapy or different regimen of NAC might have changed the results of this study, we could not discuss about it from the results of this study. Third, the frequency of the excluded patients [6 patients (18.2%)] was relatively high in this study with the small sample size. Moreover, among them, 2 patients were excluded because of gait disturbances. This might introduce a potential of selection bias, because the finally analyzed patients were limited to the patients with relatively better condition. The fourth limitation was the assessment of physical activity. The Japanese short version of IPAQ is validated and reliable. However, it is not a direct assessment tool of real physical activity, such as daily walking steps.[22,23] Thus, it should be noted that the IPAQ data alone were

TABLE 2. Changes in Weight, Physical Fitness Data, and Physical Activity Over the Course of NAC Treatment

	Pre-NAC	Post-NAC	*P*
Weight (kg)	57.5±11.8	56.5±11.6	NS
Physical fitness			
Knee extensor muscles strength (N m/kg)	2.5±0.6	2.4±0.5	NS
6-min walk distance (m)	574.9±77.8	565.1±75.3	NS
Physical activity			
IPAQ (METs min/d)	119.1 (0-605.6)	99 (0-819)	NS

Weight and physical fitness values expressed as mean±SD. IPAQ values expressed as median (range).
IPAQ, indicates International Physical Activity Questionnaire; MET, metabolic equivalent; NAC, neoadjuvant chemotherapy; NS, not significant.

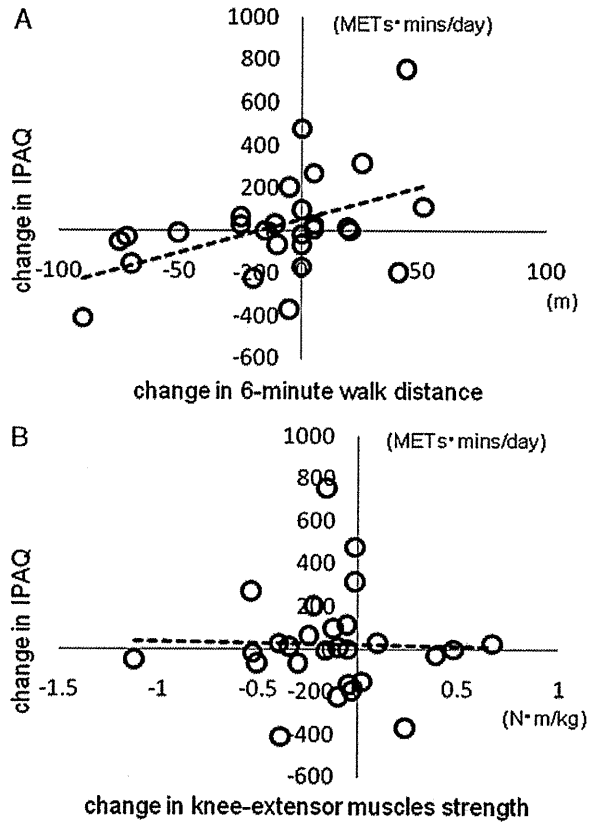

FIGURE 1. Relationship between changes in physical activity and changes in physical fitness. The change in 6-minute walking distance was correlated positively with the change in International Physical Activity Questionnaire (IPAQ) ($r=0.45$, $P=0.02$) (A), whereas the change in knee extensor muscle strength had no correlation ($r=-0.01$, $P=0.95$) (B). METs indicate metabolic equivalent.

probably insufficient to draw definitive conclusions that patients maintained their physical activity levels during NAC.

In conclusion, NAC had no impact on physical fitness, physical activity, and HRQOL in patients with ESCC. The results of this study indicated that there was no need to implement a physiotherapy intervention during NAC to prevent a decline in these parameters. As the number of patients was rather small, and the assessment tool used was insufficient, further study of a larger number of cases with more quantitative assessment tools is required to confirm the impact of NAC on physical fitness, physical activity, and HRQOL.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of all study participants.

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Macroscopic estimation of submucosal invasion in the esophagus

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KEYWORDS:
EUS;
Esophageal cancer;
Submucosal invasion

In esophageal squamous cell carcinoma, the depth of invasion into the wall is closely associated with metastasis to lymph nodes. Esophageal cancer invading the muscularis mucosae could be curably treated by endoscopic submucosal dissection but cancer with submucosal invasion necessitates surgical resection and/or chemoradiotherapy. Therefore, pretreatment diagnosis of invasion depth is crucially important for selecting appropriate treatment strategies for each individual patient. To estimate the depth of cancer invasion for early squamous cell carcinoma of the esophagus, standard endoscopy with image enhancement and endoscopic ultrasound are currently considered the best methods.

According to the staging manual published by the American Joint Committee on Cancer,[1] cancer confined to the mucosa or the muscularis mucosae is categorized as mucosal cancer (T1a). T1a esophageal cancer comprises carcinoma in situ (high-grade intraepithelial neoplasia), cancer invading the lamina propria mucosae, and cancer invading the muscularis mucosae. T1b cancer includes cancer with submucosal invasion.

In esophageal squamous cell carcinoma, the depth of invasion into the wall is closely associated with metastasis to lymph nodes (Figure 1).[2] It is important to note that the frequency of metastasis in the lymph nodes in cancer confined to the mucosa is not zero, but 3%. The risk increases to 12% in cancer invading the muscularis mucosae and markedly increases to 26%-46% in patients with submucosal invasion. Because cancers confined to the mucosal layer correlate with a low frequency of metastasis and because surgery confers a high risk of morbidity and mortality, they are considered excellent candidates for minimally invasive treatment by endoscopic mucosal resection or endoscopic submucosal dissection (ESD). Cancer invading the muscularis mucosae may still be treated by ESD, but cancer with submucosal invasion necessitates surgical resection and/or chemoradiotherapy.[3,4] Given that endoscopic resection has some risks of bleeding and perforation, pretreatment diagnosis of invasion depth is crucial for selecting appropriate treatment strategies for each individual patient.

To estimate the depth of cancer invasion for early squamous cell carcinoma of the esophagus, standard endoscopy with image enhancement and endoscopic ultrasound (EUS) are considered the best methods. Other methods such as the "barium meal," computed tomography, and positron emission tomography[5] are considered less accurate.

Indications

Conventional endoscopy with image-enhanced endoscopy is quite accurate to diagnose cancer in situ (high grade-intraepithelial neoplasia) or cancer with minimal subepithelial invasion[6,7]; in those cases, EUS is rarely indicated. In our practice, we used high-magnification endoscopy with narrow-band imaging to view the surface

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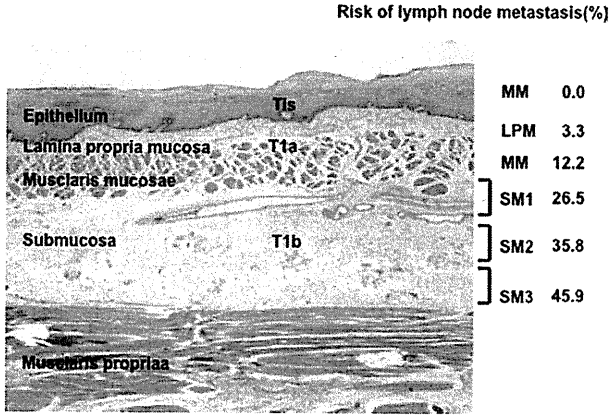

Figure 1 Risk of lymph node metastasis in the esophagus. In esophageal squamous cell carcinoma, the depth of invasion into the wall is closely associated with an increasing risk of lymph node metastasis. (Color figure is available online at www.techgiendoscopy.com.)

microvessels of early esophageal carcinoma. The patterns of these surface microvessels—called intraepithelial papillary capillary loops (IPCL)—have been shown to be predictive of the degree of mucosal and submucosal invasion.[8]

IPCL can be classified into eight different patterns; thus, the use of IPCL classification can be complex. A simpler way might be to classify the IPCL as regular and irregular. Early squamous cell carcinoma typically appears as a patch of mucosa with irregular IPCLs, which is clearly demarcated from the surrounding normal mucosa with regular IPCLs. When the carcinoma is limited to the mucosa, its surface is typically smooth and pliable. When the carcinoma has invaded the submucosa, its surface has nodular elevation, reddishness, and deeper depression. EUS can be helpful in these cases to rule out deeply submucosal invasive cancers.

Preparation

When peristalsis interferes with observation, an antispasmodic agent is required. Sedation is also necessary for stable observation.

Instruments

To visualize the distinct tissue layer of the esophageal wall, 20- or 30-MHz miniature probes should be used. This high-resolution imaging demonstrates 9-layered echo structures (Figure 2). Generally, the tumor can be seen as a low echoic mass by EUS. If the cancerous lesion invades to the submucosal layer, EUS deliver a low echoic mass in the high echo layer corresponding to the submucosal layer. A balloon can be attached to the tip of the endoscope to keep deaerated water in the esophageal lumen and prevent regurgitation to the pharynx. An endoscope with a water jet function is desirable to keep the esophageal lumen distended to obtain a clear image.

Techniques

To obtain clear images, several useful methods have been formulated. The most important issue is to keep air or air bubbles away from the scanning site.

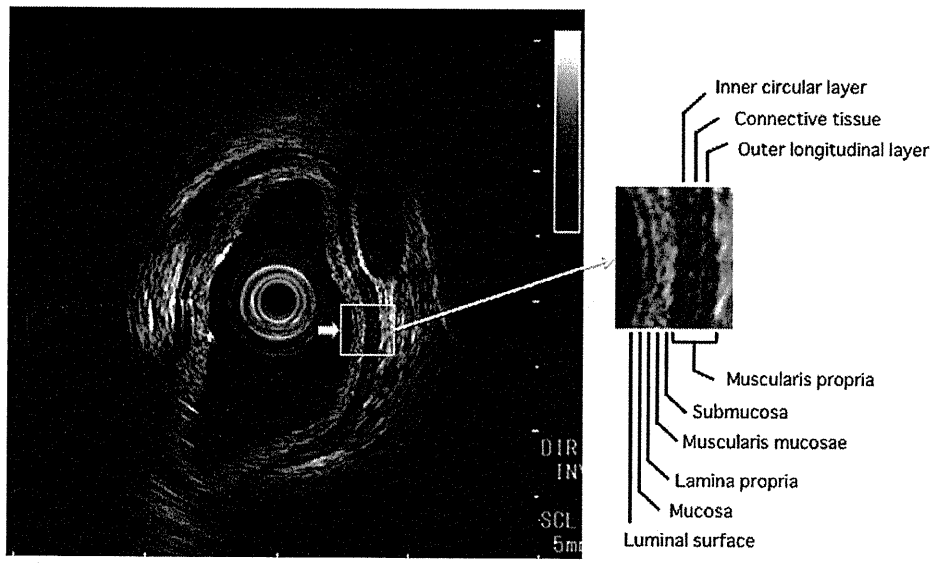

Figure 2 EUS image of the normal esophageal wall by 20-MHz miniprobe demonstrates 9-layered structures (arrow). The first 5 layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), and submucosa (high echo). Next are the inner circular (low echo) and outer longitudinal layers (low echo) of the muscularis propria. They are separated by a thin hyperechoic layer of connective tissue (high echo).

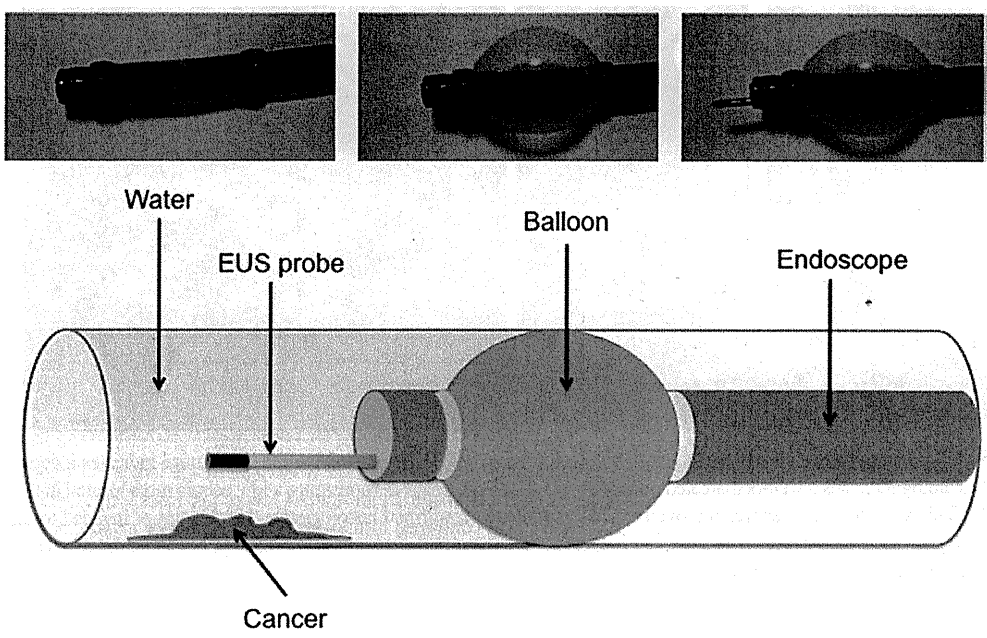

Figure 3 Photographs and scheme of EUS using the balloon method. To keep deaerated water in the esophageal lumen and prevent regurgitation to the pharynx, a balloon should be attached the endoscope itself. After insertion of the endoscope, the tip of endoscope should be directed toward the lesion. At the best position, the balloon should be dilated. With sufficient dilation of the balloon, deaerated water fills the esophageal lumen using the water jet function of the endoscope. Thereafter, scanning of the lesion will be started with a miniature probe. (Color figure is available online at www.techgiendoscopy.com.)

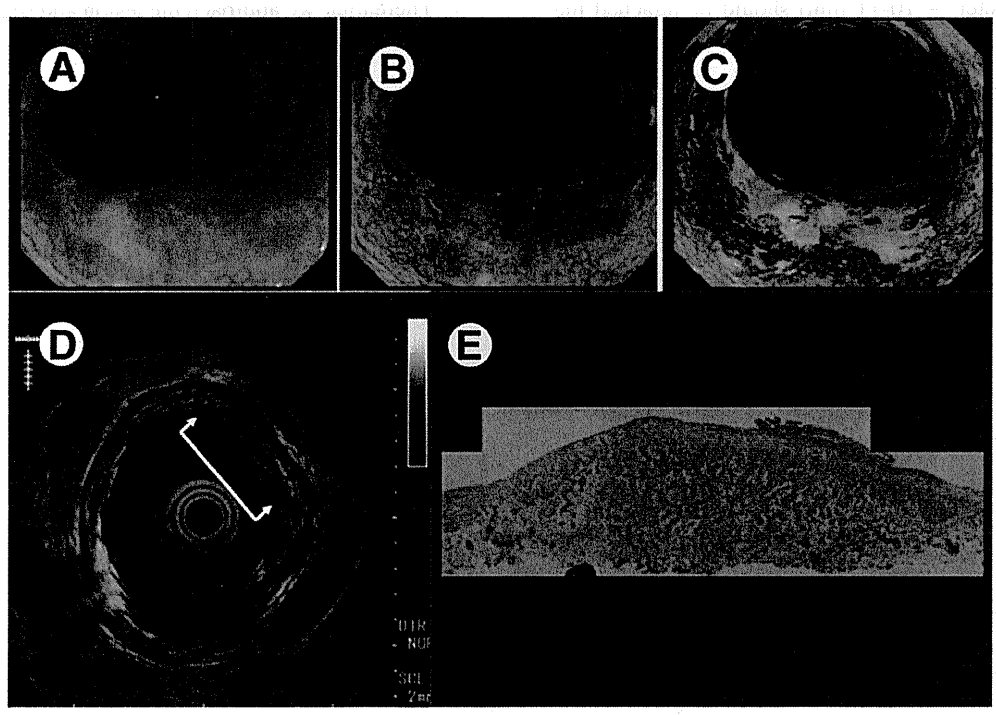

Figure 4 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image shows a reddish area. (B) Narrow-band imaging indicates a well-demarcated brownish area with a white coat. (C) Lugol's staining indicates a well-demarcated unstained area. (D) EUS image demonstrates a low echoic mass located in the submucosal layer (arrow). (E) This superficial cancer was removed by ESD and submucosal invasion of the cancer was confirmed histologically. (Color figure is available online at www.techgiendoscopy.com.)

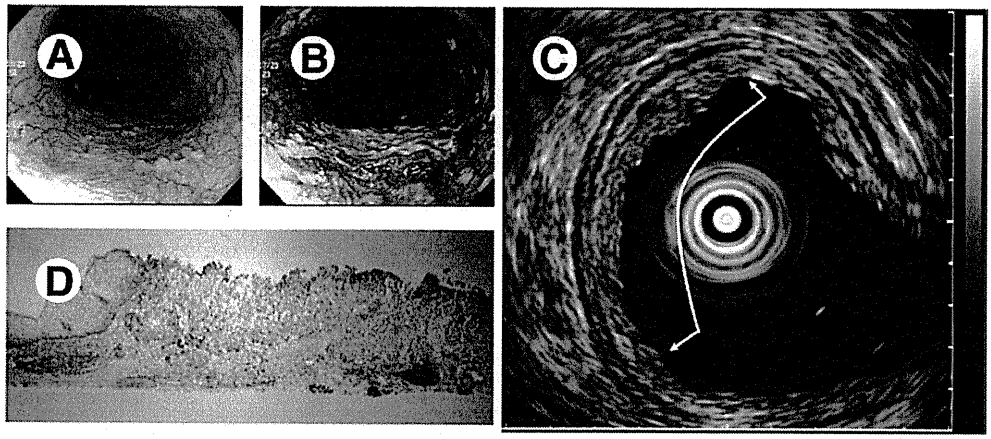

Figure 5 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image indicates a depressed reddish area. (B) Lugol's staining indicates a well-demarcated unstained area. (C) EUS image demonstrates a low echoic mass located in the submucosal layer (arrow). (D) This superficial cancer was removed by ESD and it was confirmed histologically that this tumor invaded to the muscularis mucosae but not into the submucosal layer. This case was suspected to have submucosal invasion clinically; however, the depth of invasion was histologically confirmed as mucosal cancer. (Color figure is available online at www.techgiendoscopy.com.)

Balloon method

The balloon method (Figure 3) is the generalized method. A balloon of a size that fits the endoscope should be selected.

1. To keep deaerated water in the esophageal lumen and prevent regurgitation to the pharynx, a balloon (eg, inner diameter = 10-11 mm) should be attached the endoscope itself (Figure 3A).
2. After insertion of the endoscope, we must direct the tip of the endoscope toward the lesion.
3. At the best position, the balloon should be dilated (Figure 3B).
4. With sufficient dilation of the balloon, we fill the esophageal lumen with deaerated water using the water jet function of the endoscope.
5. Thereafter, we approach the lesion and scan it with the miniature probe (Figure 3C).

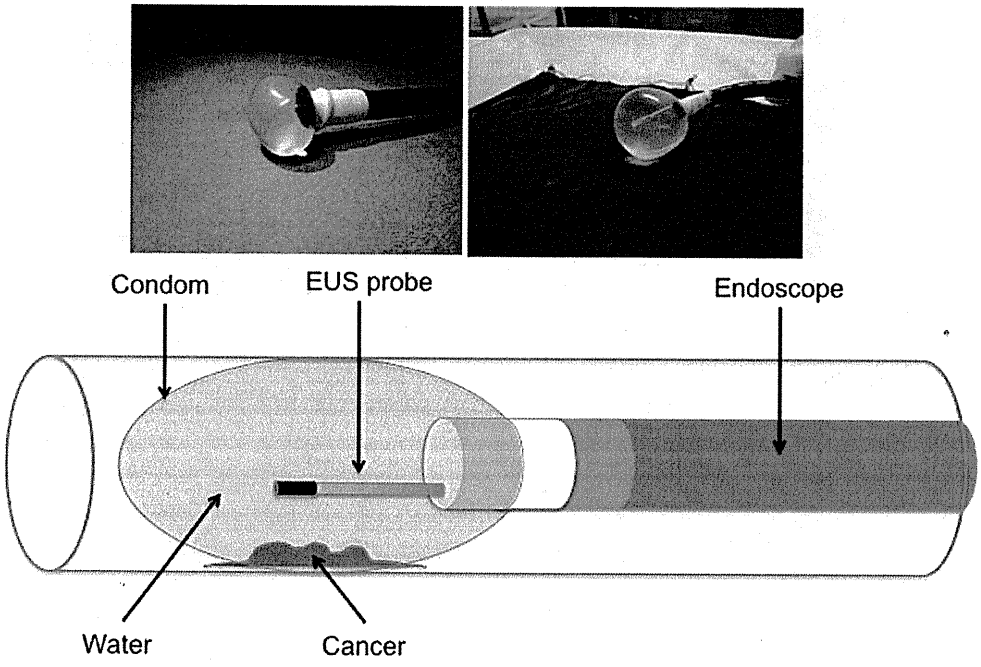

Figure 6 Photo and schema of EUS using the condom method. To keep deaerated water in the condom, a condom for gynecologic ultrasound examination should be attached to the tip of endoscope itself. (Color figure is available online at www.techgiendoscopy.com.)

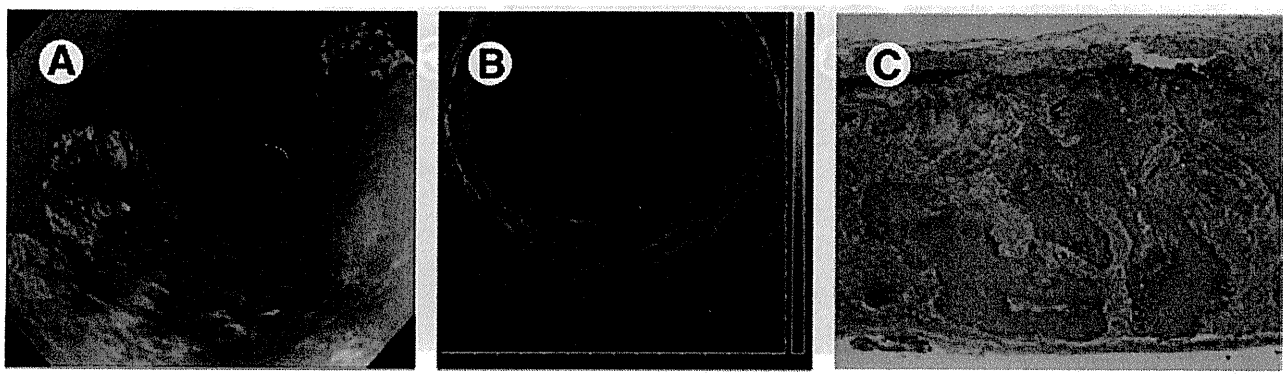

Figure 7 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image indicates a reddish area with an irregular surface. (B) EUS image indicates a low echoic mass located in the submucosal layer. (C) This superficial cancer was removed by ESD and submucosal invasion of the cancer was histologically confirmed. (Color figure is available online at www.techgiendoscopy.com.)

Sample cases are presented in Figures 4 and 5.

Condom method

Similar to the balloon method, the condom method (Figure 6) is useful to keep water in the esophageal lumen because this method can keep water in the condom itself.

A sample case is presented in Figure 7.

Echo jelly method

Echo jelly (Figure 8) is also useful to keep air away from the lesion. A sample case is presented in Figure 9.

Complications

Because the esophageal lumen is filled with deaerated water, caution must be exercised regarding aspiration caused by regurgitation. Excessive balloon expansion is a risk for esophageal injury and hemorrhage. When a patient complains of a chest pain after injection of 15-20 cc of air, the balloon is sufficiently dilated in close contact with the esophageal wall and no more pressure should be applied.

Conclusions

A completely accurate diagnosis of the depth of early esophageal carcinoma can be difficult to attain. Standard

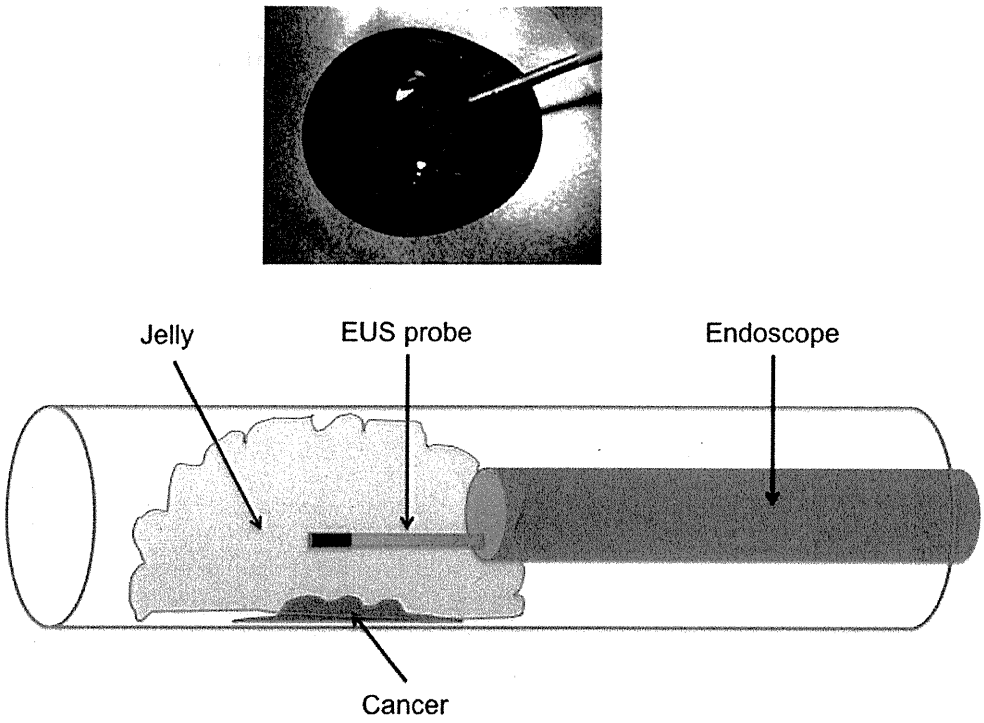

Figure 8 Schema of EUS by the jelly method. (Color figure is available online at www.techgiendoscopy.com.)

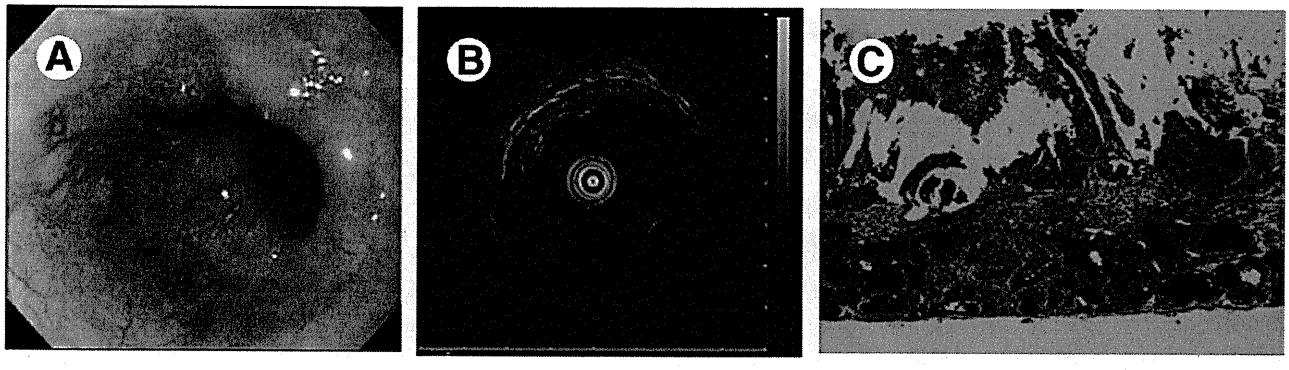

Figure 9 Superficial esophageal carcinoma (squamous cell carcinoma). (A) Conventional white light image shows a reddish area with nodular change. (B) EUS image demonstrates a low echoic mass located in the submucosal layer. (C) This superficial cancer was removed by endoscopic mucosal resection and submucosal invasion of the cancer was confirmed histologically. (Color figure is available online at www.techgiendoscopy.com.)

endoscopy with image enhancement and, if available, with high-magnification combined with EUS is useful in assessing the depth of invasion of lesions being considered for endoscopic resection. In cases treated by endoscopic mucosal resection/ESD, if the depth of invasion was found to have deeper invasion than estimated by pretreatment diagnosis, surgical resection and/or chemoradiotherapy may be necessary as an additional curative treatment. Currently, endoscopic resection is used in cases with shallower invasion. However, given of the risks of lymph node metastasis, informed consent that includes a thorough explanation of all possibilities is required.

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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

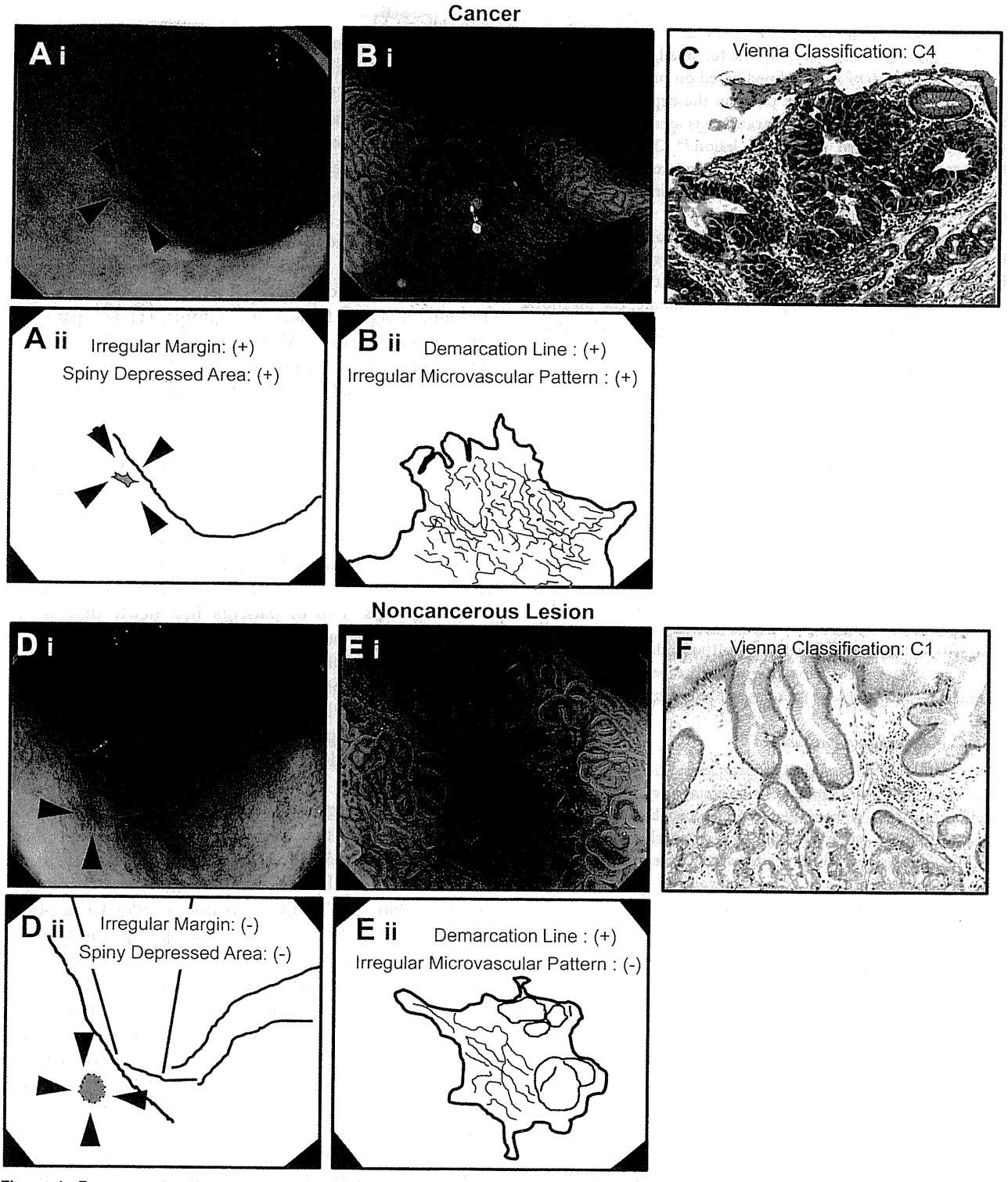

Figure 1. Representative endoscopic findings for gastric small, depressed lesions. *A–C* show a case of cancer, and *D–F* show a case of noncancerous lesions. *A* shows an endoscopic image obtained using C-WLI. A small, depressed lesion (*arrowheads*) is evident in the anterior wall of the lower part 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 χ^2 test. Analyses of the effect of additional M-NBI after the initial C-WLI on diagnostic performance were conducted using the population whose diagnoses had been confirmed by pathology and McNemar testing. Analysis of the examination duration was conducted using the population who completed protocol examination and the Mann–Whitney nonparametric test for comparisons between C-WLI and M-NBI, as well as the Wilcoxon signed rank test for comparisons between C-WLI and C-WLI plus M-NBI. All probability values calculated in this analysis were 2 sided, and $P < .05$ was considered significant.

Results

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

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

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

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

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

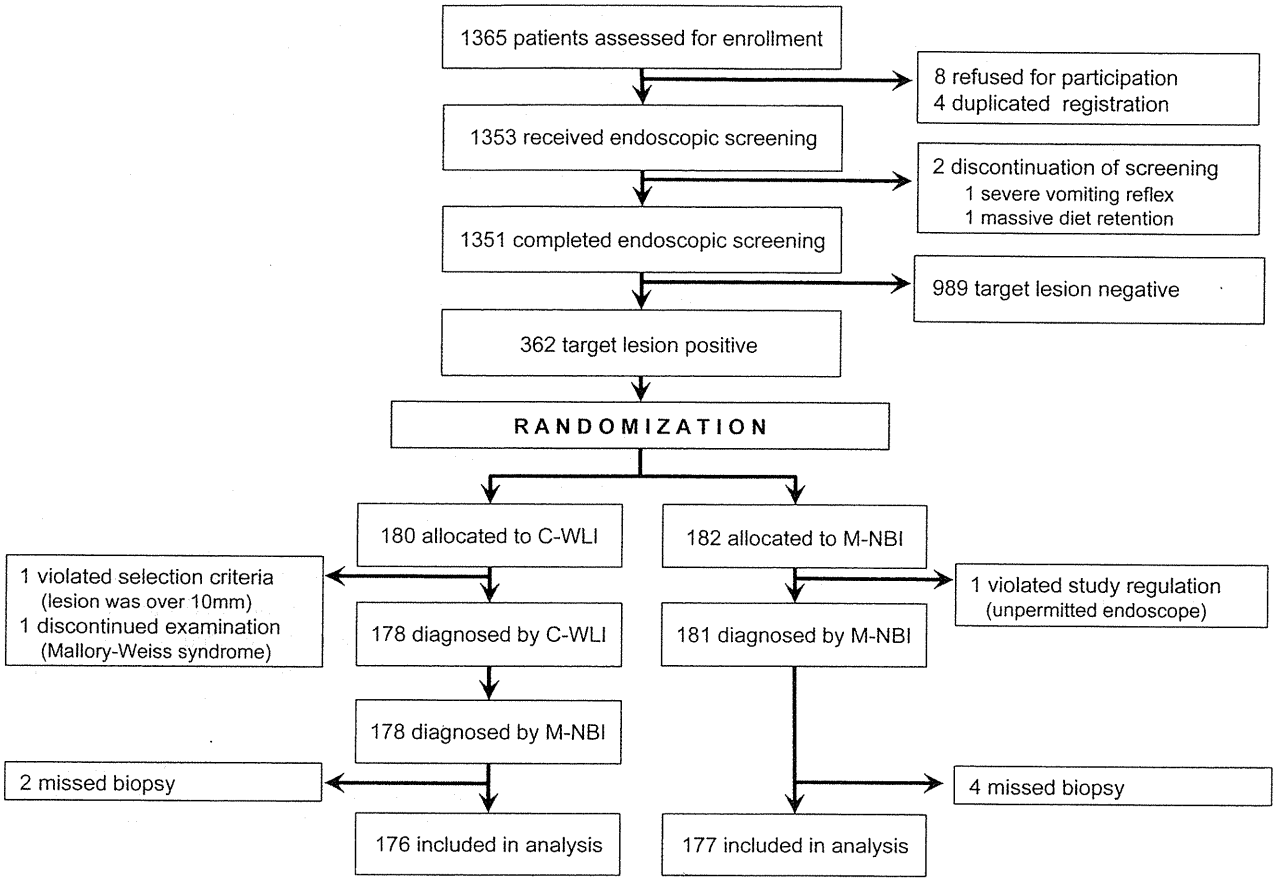

Figure 2. Patient enrollment, randomization, and examination.

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

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

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

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

Discussion

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

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

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

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

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

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

Table 2. Endoscopic Diagnoses for All Small Depressed Lesions

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