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Evaluation of a novel high-resolution magnifying videoendoscope that is capable of photodynamic diagnosis and therapy for gastric cancer

Tetsuya Nakamura MD, PhD[a,*], Takeshi Oinuma[b], Hidetsugu Yamagishi[c], Hironori Masuyama[d], Akira Terano[e]

[a] *Department of Medical Informatics (Formerly Department of Endoscopy), Dokkyo Medical University School of Medicine, 811 Kita-kobayashi, Mibu, Tochigi 321-0293, Japan*
[b] *Nigamido Medical Clinic, Japan*
[c] *Dokkyo Medical University School of Medicine, Department of Pathology, Japan*
[d] *Masuyama Gastrointestinal Clinic, Japan*
[e] *Dokkyo Group of Academic Institutions, Japan*

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Summary
Objective: To evaluate the usefulness of a novel high-resolution magnifying videoendoscope called the XG-0001 (Fujifilm, Tokyo, Japan) that is capable of PDD and PDT in experimental and clinical situations.
Materials and methods: The fluorescences of three photosensitizers (i.e., porfimer sodium (Photofrin), protoporphyrin IX and talaporfin sodium (Laserphyrin)) were studied experimentally via excitation with a purple diode laser (VDL, wavelength 405 nm). Five consecutive patients with superficial early gastric cancer not indicated for surgery or other curative endoscopic treatment due to complicated serious diseases were enrolled in this study. After close endoscopic examinations, 2 mg/kg of Photofrin were intravenously injected into the patients for PDT, and 5-aminolevulinic acid (ALA; 15–20 mg/kg) was orally taken for PDD. PDD using VDL and PDT using an excimer-dye laser (630 nm, 4 mJ, 60 Hz) were performed with the XG-0001.
Results: Photofrin and Laserphyrin had experimentally the lowest and highest fluorescence intensities, respectively. The five patients comprised four men and one woman with a mean age 75.2 year and an age range of 56–83 years. Two additional cancerous lesions were newly detected by magnifying pharmacoendoscopy. In each patient, PDD was successfully performed.

* Corresponding author. Tel.: +81 282 86 1111; fax: +81 282 86 7761.
E-mail address: nakamurt@dokkyomed.ac.jp (T. Nakamura).

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PDT could also safely performed and CR was obtained in 71.4% (5/7) of the cancerous lesions in five patients, and no serious complications were encountered.
Conclusion: The XG-0001, which is based on a simultaneous videoendoscopy method that uses an RGB color chip CCD, proved extremely useful in routine use and also in PDD and PDT for gastric cancer.

Introduction

Gastric cancer is one of the main cause of mortality not only in Japan but also in many developing countries [1]. Recently, new endoscopic treatments for early gastric cancer, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have been developed [2,3]. Furthermore, new endoscopic diagnostic procedures for early gastric cancer based on magnifying endoscopes [4] and image-enhanced endoscopies (IEEs), such as narrow-band imaging (NBI) [5] and flexible spectral imaging color enhancement (FICE) [6], have been established. Subsequently, the early detection and early treatment of gastric cancer has become possible; therefore, the mortality rate of gastric cancer is gradually decreasing. However, the limitations encountered for superficial gastric cancer patients for whom endoscopic and surgical resection are contraindicated due to serious complications remain to be addressed.

Photodynamic therapy (PDT) is defined as the use of photodynamic agents in the treatment of disease. A photodynamic agent is a substance that is activated by light to cause damage to tissue. Photodynamic agents can be exogenous and absorbed preformed from the environment or endogenous and formed within the body as an abnormal metabolite, e.g., porphyrins, or as a normal metabolite, e.g., phylloerythrin, and accumulated in tissues due to faulty excretion, e.g., in hepatic disease (Sounders Comprehensive Veterinary Dictionary, 3rd edition). Therefore, photodynamic diagnosis (PDD) is defined as the use of fluorescence detection using a photodynamic agent in the diagnosis of disease. PDT is one of the non-invasive endoscopic treatments for superficial early gastric cancer, and PDT utilizing an excimer-dye laser (EDL, Hamamatsu Photonics K.K., Hamamatsu, Japan) and porfimer sodium (Photofrin, Pfizer Japan Inc., Tokyo, Japan) is approved by the Ministry of Health, Labour and Welfare in Japan. Photofrin is a photosensitizer that consists of porphyrin compounds and is also a photodynamic agent. PDD using Photofrin to detect early-stage pulmonary tumors with purple light (405 nm wavelength) excitation has previously been reported [7]. In this manuscript, PDD is defined as a procedure that uses fluorescence detection of a photodynamic agent and purple light excitation.

We have used PDT for inoperable gastric cancer patients since 1988 [8]. However, a technical problem with PDT has existed for a long time; i.e., an optic fiberscope is needed during laser irradiation because endoscopic images changes caused by whiteout due to the intense laser light (Fig. 1A) when using a conventional videoendoscope such as the GIF Q240 (Olympus Medical Systems Corp., Tokyo, Japan). In 2003, we found that the EG-485ZH magnifying videoendoscope (Fujinon, now Fujifilm, Tokyo, Japan) could be applied to both PDT (Fig. 1B) and PDD after examination of the suitability of laser light and several videoendoscopes. In 2008, a novel high-resolution magnifying videoendoscope capable of PDD and PDT called the XG-0001 (Fujifilm, Tokyo, Japan) was developed.

The aim of the present study was to evaluate usefulness of the XG-0001 in experimental and clinical use.

Materials and methods

The novel XG-0001 high-resolution magnifying videoendoscope is based on the EG-590ZW (Fujifilm, Tokyo, Japan), which is a simultaneous method videoendoscope system that uses a red, green and blue (RGB) color chip charge coupled device (CCD). The optical magnification rate of the XG-0001 is up to 135 times on 19-inch high-definition color monitor; moreover, this endoscope is capable of 10 channels of FICE [6] as an IEE.

The study protocols were planned in accordance with the Declaration of Helsinki of 1975 and were reviewed and approved by the local ethical committee (No. 2015/2008).

Experimental PDD and PDT studies

To confirm fluorescence during PDD, we studied the three photosensitizers that are available in Japan: Photofrin, protoporphyrin IX (PpIX; SBI Pharmaceuticals Co., Ltd., Tokyo, Japan) and talaporfin sodium (Laserphyrin; Meiji Seika Pharma Co., Ltd., Tokyo, Japan). The light source was a purple diode laser (VDL, 405 nm wavelength) with a spectrometer (VDL-M1/ver.3.0SP; m & m Co., Ltd., Tokyo, Japan). The three photosensitizers were diluted to physiological concentrations that are used clinically (Photofrin: 2.5 mg/mL, PpIX: 20 nmol/L, Laserphyrin: 25 mg/mL) and dropped onto black sponges. During irradiation with the VDL via the XG-0001, fluorescence on the sponge was observed on a 19-inch high-definition color monitor, digital pictures and videos were recorded. Simultaneously, the spectrum of each photosensitizer was measured with a spectrometer. We also examined which FICE channel enhanced the fluorescence by PDD.

To determine the best conditions for the XG-0001 during PDT, we adjusted the pulse rate of the EDL and the shutter speed of this novel endoscope. Additionally, we determined which FICE channel best minimized the brightness on the color monitor due to the intense laser light during PDT.

Clinical study

Five consecutive patients with superficial early gastric cancer not indicated for surgery or other curative endoscopic

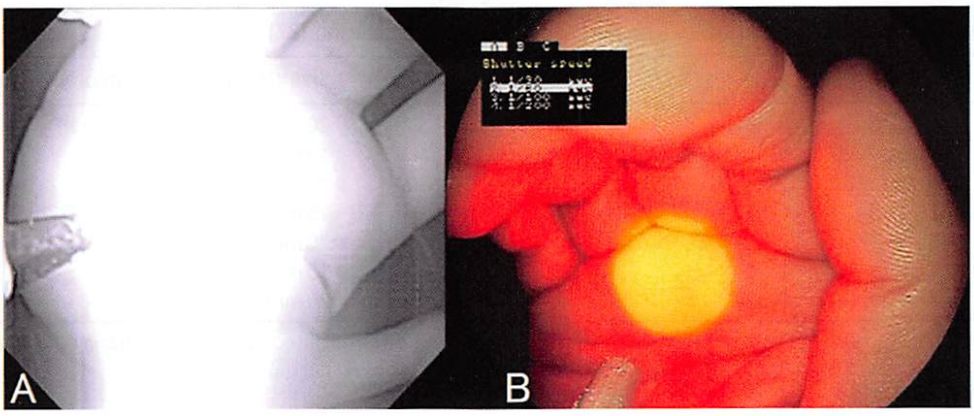

Fig. 1 Comparison of two types of videoendoscopes during laser irradiation. (A) A field sequential method videoendoscope with a monochrome CCD and a rotation disk with red, green and blue (RGB) optical filters (GIF Q240, Olympus). (B) A simultaneous method videoendoscope with a RGB color chip CCD (EG-485ZH, Fujifilm).

treatments, such as EMR and ESD, due to complicated serious diseases, such as heart failure, renal failure, etc., were enrolled in this study between June of 2008 and July of 2009. Before PDD and PDT, close endoscopic examinations that included endoscopic ultrasoundscopy (EUS), magnifying pharmacoendoscopy [9] and chromoendoscopy using indigo carmine dye were performed with the EG-590ZW or XG-0001. At that time, biopsies were carried out from the localized area of gastric cancer.

On the afternoon of the day of admission day (the 1st day), 2 mg/kg of Photofrin was intravenously injected into the patient, and the patient was subsequently protected from sunlight. On the morning of the 3rd day, the patient consumed four soft capsules containing 250 mg of 5-aminolevulinic acid (ALA; 15–20 mg/kg, SBI Pharmaceuticals Co., Ltd., Tokyo, Japan) with some water; these capsules dissolved in the small intestine. Because the fluorescence of Photofrin was very weak in the experimental study (Fig. 2A), it was thought to be inapplicable for PDD in the clinical study. Thus, the 5-ALA was used for the PDD. Four or five hours after the administration of the 5-ALA, PDD using the VDL-M1/ver.3.0SP (405 nm, 80–100 mW) and the XG-0001 was performed. Immediately after the detection of fluorescence and the measurement of the spectrum, PDT using EDL (630 nm, 4 mJ, 60 Hz; equal to 240 mW) with the XG-0001 was performed. Regarding the PDT, the target dose of irradiation was set to 60–100 J/cm^2, and we used a free-cut quartz fiber or cylindrical quartz fiber when the cancerous lesion was the excavated type. On the afternoon of the 4th day, additional EDL irradiation was provided if the treatment of the cancerous lesion was insufficient based on magnified observations with the XG-0001. On the morning

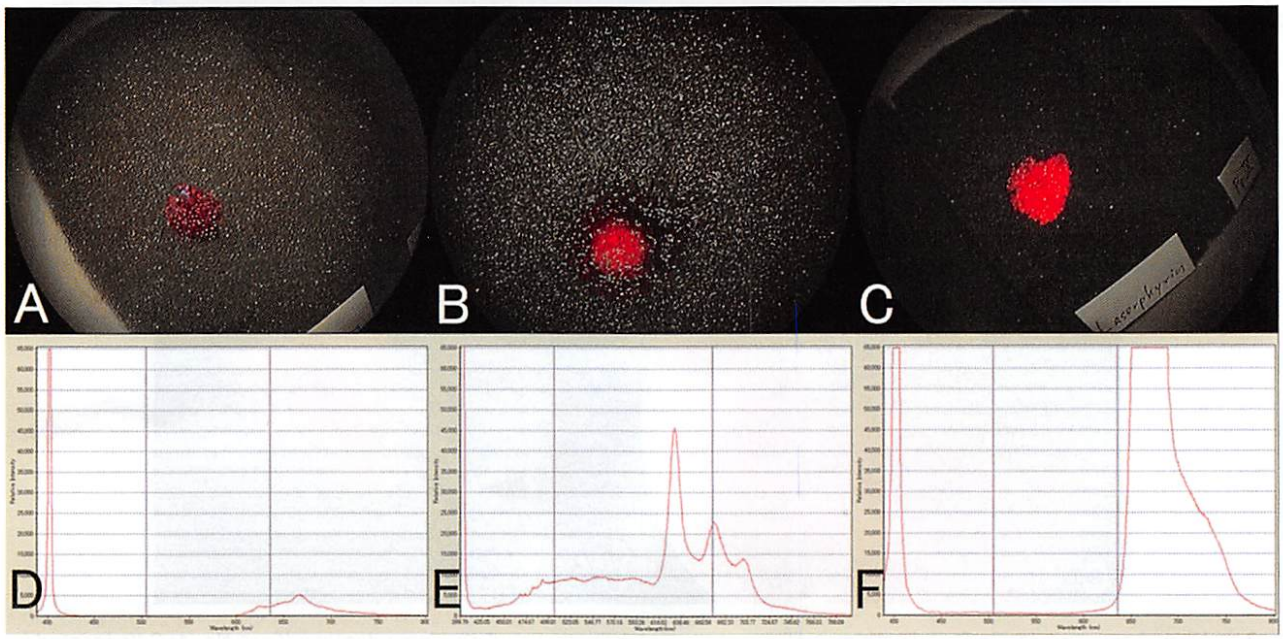

Fig. 2 Detection of fluorescence with the novel high-resolution videoendoscope (XG-0001, Fujifilm). Endoscopic fluorescence images: (A) porfimer sodium (Photofrin), (B) protoporphyrin IX (PpIX), (C) talaporfin sodium (Laserphyrin). Fluorescence emission spectra: (D) Photofrin, (E) PpIX, (F) Laserphyrin.

Table 1 Patient characteristics and results (the Paris endoscopic classification [27] was applied).

No.	Sex/age	Location	Type (Paris class)	Histology	Depth	Size (Max)	PDT outcome	Survival duration
1	M/76	Body GC	0-IIc+IIa	Well–Mod.	SM	20 mm	CR	6 years 1 month
		Antrum LC	0-IIa	Well–Mod.	M	15 mm	CR	
2	M/56	Antrum GC	0-IIc+IIa	Well	SM	10 mm	CR	6 years 1 month
3	M/81	Fundus GC	0-IIa+IIc	Well	SM	15 mm	CR	5 years 10 months
4	F/83	Body PW	0-IIc	Mod.	SM	20 mm	PR	5 years 4 months
		Fundus PW	0-IIc	Well	M	15 mm	CR	
5	M/80	Antrum GC	0-IIa	Well	SM	20 mm	PR[a]	5 years 1 month

GC, greater curvature; LC, lesser curvature; PW, posterior wall; Well, well differentiated adenocarcinoma; Mod., moderately differentiated adenocarcinoma; SM, submucosal; M, mucosal; CR, complete remission; PR, partial remission.
[a] CR by additional PDT.

of the 11th day (7 days after PDT), magnified observations were made with the XG-0001 or EG-590ZW. If the laser ulcers were in the healing stage and free of hemorrhage and there were no symptoms, the patient was discharged on the evening of the 12th day. Laboratory data (before, immediately after and three months after treatment) were compared, and the patients' symptoms, including as sunburn, stomachache and appetite loss, were observed. At three months after treatment, magnified observations and punch biopsies of the treated lesions with the XG-0001 or EG-590ZW were performed. Complete responses (CR) and partial responses (PR) were defined as the absence of any detected cancer and some detected cancer, respectively, at three months after PDT. After treatment, the patients were followed up regularly as long as possible. This study was approved by the local ethical committee (No. 2015/2008).

Results

Experimental PDD and PDT studies

Red color fluorescence was clearly observed from every photosensitizer following VDL irradiation via the XG-0001 (Fig. 2A: Photofrin, Fig. 2B: PpIX, Fig. 2C: Laserphyrin). Additionally, every fluorescence spectrum exhibited the characteristic spectrum the corresponding photosensitizer (Fig. 2D: Photofrin, Fig. 2E: PpIX, Fig. 2F: Laserphyrin). Photofrin had the lowest and Laserphyrin had the highest

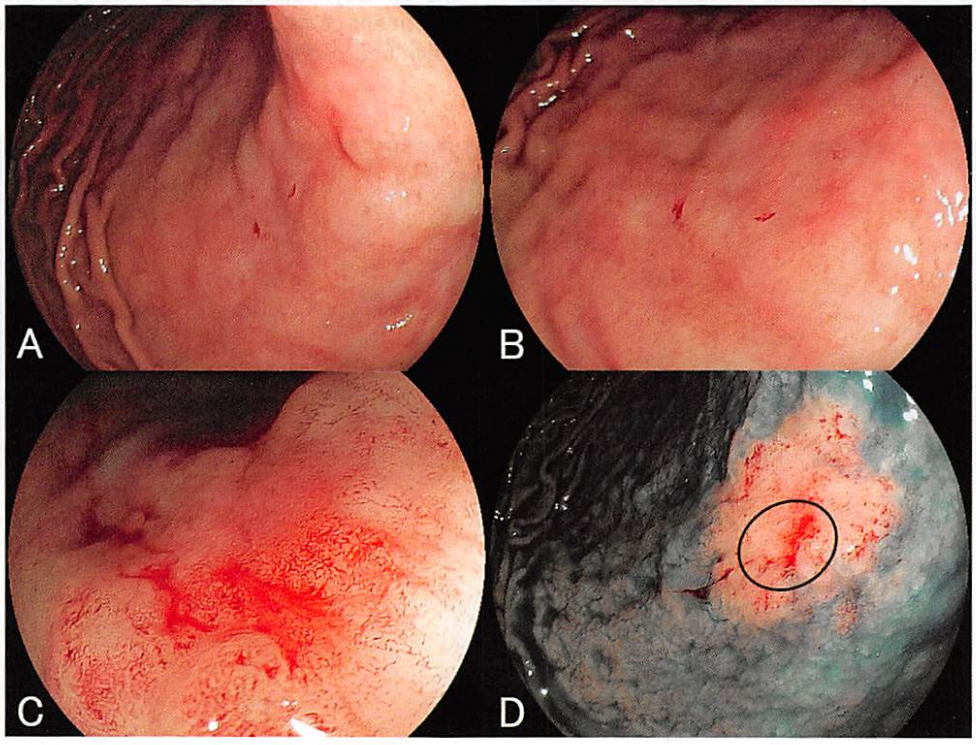

Fig. 3 A new cancerous lesion found with magnifying pharmacoendoscopy and chromoendoscopy (Case No. 4; 0-IIc located in the posterior wall of the fundus, shown in Table 1). (A) Endoscopic view of the posterior wall of the fundus. (B) Close view of the same area. (C) Magnified view just after spraying epinephrine solution (0.05 mg/mL). (D) Endoscopic view of the same area as C (circled) via chromoendoscopy using indigo carmine dye.

fluorescence intensities (Fig. 2). No available FICE channel enhanced the PDD fluorescence.

During the irradiation, the pulse frequency of the EDL was adjusted to 60 Hz, and the shutter speed of the XG-0001 was adjusted to 1/60 s to achieve the maximal prevention of whiteout on the monitor. The channel 2 FICE settings (R: 550 nm, G: 500 nm, B: 450 nm) were optimal for minimizing the brightness due to the laser light.

Clinical study

The characteristics of five patients and the results of the clinical study are summarized in Table 1. The five patients comprised four men and one woman with a mean age of 75.2 years and an age range of 56–83 years. Before PDT, two additional cancerous lesions (Case No. 1; 0-IIa located in the lessor curve of the antrum; Case No. 4; 0-IIc located in the posterior wall of the fundus, Fig. 3) were found via close endoscopic examinations that included magnified pharmacoendoscopy [9] and chromoendoscopy.

In each patient, PDD (i.e., the detection of fluorescence and the fluorescence spectrum) was successful on the 3rd day and was unsuccessful on the 4th day. The detected fluorescence of Case No. 1 (0-IIc+IIa located in body of the greater curve) is shown in Fig. 4A, and its emission spectrum is shown in Fig. 4B.

In PDT, CR was obtained in 71.4% (5/7) of the cancerous lesions in five patients. The treatment course of a metachronous superficial early gastric cancer after ESD located in the greater curvature of the gastric body (Case No. 1 in Table 1) is shown in Fig. 5 (A: before PDT, B: during irradiation, C: one week after PDT, and D: six months after PDT). The PR of the cancerous lesion of patient No. 5 was altered to CR following an additional course of PDT. Patient No. 4 refused additional treatment due to the absence of symptoms following the first course of PDT.

Slight liver dysfunctions occurred in two patients but recovered within a week. Reversible sunburn due to photosensitivity was observed in two patients. However, no serious complications, such as hemorrhage, peritonitis or perforation of the stomach, were encountered.

As on August of 2014 every patient has survived, and the range of survival durations is 5 years 1 month to 6 years 1 month.

Discussion

Experimental studies and clinical experiences showed that the novel XG-0001 high-resolution magnifying videoendoscope was capable of performing not only PDD but also PDT for gastric cancer.

As mentioned in ''Introduction'' section, the requirement of an optic fiberscope during PDT because the endoscopic image is altered by whiteout due to the intense laser light during the use of conventional videoendoscope has been a technical problem in Japan (Fig. 1A). There are two different types of videoendoscope systems. The first is a sequential method system that involves a xenon lamp, a monochrome CCD and a rotation disk with RGB optical filters. The second is a simultaneous method system that involves a xenon lamp and a RGB color chip CCD. The former

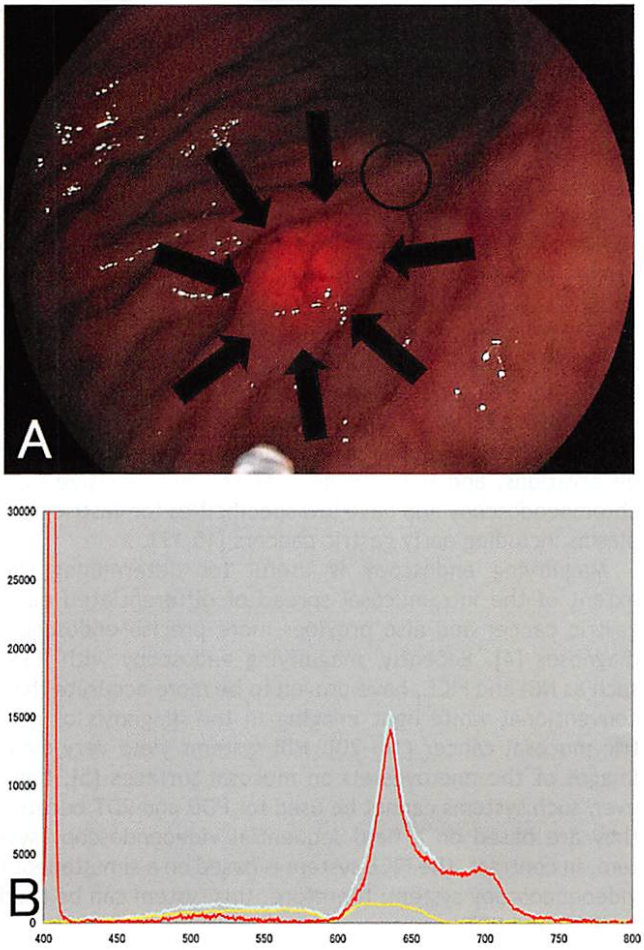

Fig. 4 Detection of fluorescence in vivo (superficial early gastric cancerous lesion located in the greater curvature of the gastric body; Case No. 1, shown in Table 1). (A) Endoscopic image: 0-IIa+IIc (indicated by arrows) and a scar after ESD (circled). (B) Fluorescence emission spectra (light blue: total spectrum, yellow: background spectrum, red: true spectrum).

type of system is produced by Olympus as the EVIS-200 series and is sold mainly in Japan, China, Korea and the United Kingdom (UK). The latter systems are also produced by Olympus as the EVIS-100 series and are sold all over the world with the exceptions of Japan, China, Korea and the UK. In contrast, all of the videoendoscope systems produce by Fujifilm and Pentax are the simultaneous type. Because the EVIS-200 series videoendoscopy system is very popular in Japan, we had been using an optic fiberscope and TV system during PDT for gastric cancer [10]. However, we found that the simultaneous videoendoscope method is capable of observing of laser irradiation (Fig. 1B). We thought that the simultaneous videoendoscope method with a sharp-cut filter including 405 nm could be used to perform PDD. Then, we decided to develop the XG-0001, which is based on the commercially available EG-590ZW model. Despite the sharp-cut filter, there were no differences in endoscopic color tone between the XG-0001 and EG-590ZW.

Fluorescence diagnosis has become important in clinical practice, particularly in the identification and localization of pre- and early cancerous lesions and image-guided therapy [11]. There are two types of fluorescence diagnostic

methods. The first is exogenous drug-induced fluorescence (including PDD), and the second is autofluorescence (AF). Exogenous 5-ALA is a natural precursor of the heme biosynthetic pathway; therefore, it induces the formation of PpIX, which is an endogenous photosensitizer (photodynamic agent) [12]. Attempts to apply PDD to gastric cancer with 5-ALA have previously been reported; however, the resulting endoscopic images were poor due to the use of optic fiberscopes [13,14]. There are two types of AF videoendoscopy system in the field of gastrointestinal endoscopy. The first include the light-induced fluorescence endoscope (LIFE; Xillix Technologies Corp., Richmond, British Columbia, Canada; and Olympus Medical Systems Corp., Tokyo, Japan) systems [15,16], the second include the SAFE-3000 system (HOYA Corporation, Tokyo, Japan) [17]. Unfortunately, neither the LIFE nor the SAFE-3000 system can be used for magnified observations, and these techniques are less sensitive than chromoendoscopy and have low specificities for gastric neoplasias including early gastric cancers [15,17].

Magnifying endoscopy is useful for determining the extent of the intramucosal spread of differentiated early gastric cancer and also provides more precise endoscopic diagnoses [4]. Recently, magnifying endoscopy with IEEs, such as NBI and FICE, have proven to be more accurate than conventional white-light imaging in the diagnosis of gastric mucosal cancer [18–20]. NBI systems yield very clear images of the microvessels on mucosal surfaces [5]; however, such systems cannot be used for PDD and PDT because they are based on a field sequential videoendoscopy system. In contrast, the FICE system is based on a simultaneous videoendoscopy system; therefore, this system can be used for PDD and PDT.

PDT is a non-invasive light-based oncologic intervention, and its fundamental principle is as follows. A photosensitizer, such as Photofrin, is applied and then activated by light of the appropriate wavelength and intensity from a source such as an EDL (630 nm); this creates the photodynamic reaction that ablated the tumor and vasculature [21]. Upon the photodynamic reaction, the production of singlet oxygen and other reactive chemical radicals causes local nonthermal cellular damage, vascular thrombosis, and necrosis, which evolve over hours to several days [22,23]. Systemic administration of 5-ALA has been employed in numerous studies of PDT for ablation of Barrett's mucosa. Potential advantage of 5-ALA is specifically for Barrett's esophagus include greater mucosal concentrations compared to submucosal and stromal levels (yielding more superficial injury). When given orally it yields peak levels of PpIX in the esophageal mucosa in 4–6 h [23]. In our study, PDT was performed after the administration of 5-ALA and Photofrin, and Photofrin mainly caused a tumor response by PDT. After the administration of Photofrin, it is cleared from most tissues over 40–72 h but retained for longer intervals in tumors, skin, and the reticuloendothelial system [23]. After several clinical studies [24,25], Photofrin PDT was approved for superficial early gastric cancer, and this treatment is covered by the public health insurance system of Japan. The term ''early gastric cancer'', defined in 1971 by the Japanese Society of Gastroenterology and Endoscopy as carcinoma limited to gastric mucosa and or submucosa regardless of lymph node status [26]. Indications for Photofrin PDT are superficial early gastric cancers that have invaded the submucosal layer and are approximately 1–3 cm in diameter without ulcerations, or under 2 cm in

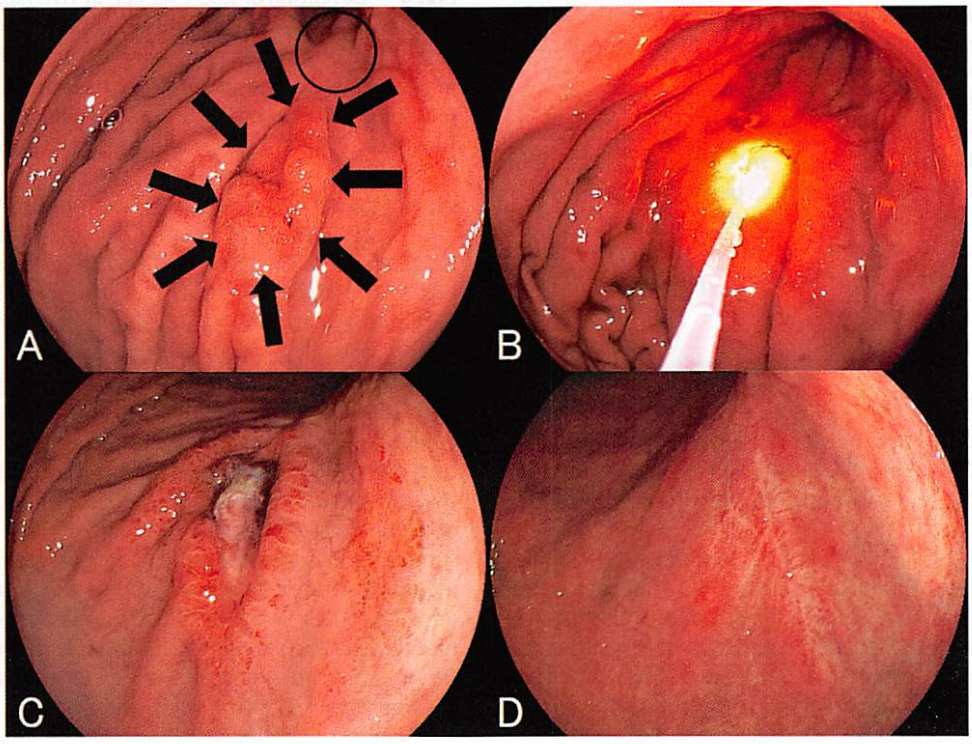

Fig. 5 The treatment course of a metachronous superficial early gastric cancer after ESD located in the greater curvature of the gastric body (Case No. 1 in Table 1). (A) Before PDT:0-IIa+IIc (indicated by arrows) and a scar after ESD (circled). (B) During irradiation with an EDL using cylindrical quartz fiber. (C) One week after PDT. (D) Six months after PDT.

diameter with ulcerations. The target patients are those with contraindications for surgery or curative endoscopic treatments, such as EMR and ESD, without metastases to the lymph nodes according to diagnostic imaging. As a result of the recent advances in endoscopic diagnostic and treatment techniques for superficial gastric cancer, PDT has come to be regarded as a supplementary ablation treatment [27] and has become unpopular.

The novel XG-0001 videoendoscope has several characteristics. First, this videoendoscope is capable of PDD (Figs. 2 and 4) without special system such as the SAFE-3000. In contrast to the AF method, PDD relies on the selective uptake and retention of photosensitizers by abnormal tissue to generate image contrast, and PDD generally produces greater intensity contrasts than AF and displays characteristic spectral features [11]. In the field of bronchoscopy, the SAFE-3000 system can be used with Laserphyrin for PDD for the early detection of centrally located early lung cancer [28]. Unfortunately, the SAFE-3000 system with Laserphyrin is not currently approved for gastric cancer in Japan. Photofrin PDT should be avoided due to the possibilities of photosensitivity and liver dysfunction. In the near future, PDD with Laserphyrin for gastric cancer might be realized, and this problem will be solved. The possibilities of magnified observation during PDD and the enhancement of fluorescence by FICE will also be realized.

The capacity for magnified observation with FICE is another merit of the XG-0001. Magnified observation of microvessels on mucosal surfaces is useful for the early detection of differentiated types of gastric cancer [4]. When epinephrine is applied, the noncancerous gastric mucosa surrounding a cancerous lesion changes in color from red to white, and no microvessels are evident. In contrast, cancerous lesions exhibit clear enhancement of the tumor microvessels [9]. This technique is termed magnifying pharmacoendoscopy and can be applied to every type of magnifying endoscopy. In the present study, this technique was useful for identifying two additional cancerous lesions (Case No. 1; 0-IIa located in the lessor curve of the antrum and Case No. 4; 0-IIc located in the posterior wall of the fundus; Fig. 3). Magnified observations during the interval of PDT revealed edematous changes and vascular shutdown of the microvessels in the irradiated lesions.

During PDD and PDT, laser light was observable on a 19-inch high-definition color monitor without sunglasses (Figs. 4A and 5B). Moreover, the channel 2 setting of the FICE minimized the brightness of the laser light. In situations involving pulsed wave lasers, adjustments of the pulse frequency and the shutter speed of the endoscope were needed. Regarding the efficacy of Photofrin PDT, CR was obtained in 71.4% (5/7) of the cancerous lesions in five patients (Table 1). This result is not significantly different from those of previous reports [24,25]. However, all of the patients lived for at least five years after PDT, and they had maintained their quality of life. This method may be applicable also on the treatment of superficial esophageal cancer.

To our knowledge, no high-resolution magnifying videoendoscope that is capable of PDD and PDT such as the XG-0001 has previously been developed.

Conclusion

The novel high-resolution XG-0001 magnifying videoendoscope, which is based on a simultaneous videoendoscope method that utilizes a RGB color chip CCD, proved to be extremely useful not only for routine use but also for PDD and PDT, particularly in cases of gastric cancer.

Conflict of interest

None of authors have any conflicts of interest or competing financial interests.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: Cancer J Clin 2011;61:69–90.
[2] Kawaguchi M, Misaka R, Yamada M, Midorikawa S, Sanji T, Shinohara S, et al. Electronic endoscopy in endoscopic mucosal resection (EMR) of gastric cancer. Diagn Ther Endosc 1995;1:209–16.
[3] Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006;41:929–42.
[4] Yao K, Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. Gastrointest Endosc 2002;56:279–84.
[5] Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). Endoscopy 2004;36:1080–4.
[6] Osawa H, Yoshizawa M, Yamamoto H, Kita H, Satoh K, Ohnishi H, et al. Optimal band imaging system can facilitate detection of changes in depressed-type early gastric cancer. Gastrointest Endosc 2008;67:226–34.
[7] Lam S, Palcic B, McLean D, Hung J, Korbelik M, Profio AE. Detection of early lung cancer using low dose Photofrin II. Chest 1990;97:333–7.
[8] Nakamura T, Ejiri M, Fujisawa T, Akiyama H, Ejiri K, Ishida M, et al. Photodynamic therapy for early gastric cancer using a pulsed gold vapor laser. J Clin Laser Med Surg 1990;8:63–7.
[9] Fukui H, Shirakawa K, Nakamura T, Suzuki K, Masuyama H, Fujimori T, et al. Magnifying pharmacoendoscopy: response of microvessels to epinephrine stimulation in differentiated early gastric cancers. Gastrointest Endosc 2006;64:40–4.
[10] Mimura S, Narahara H, Murakami T, Otani T, Hirano T, Suzuki K. A new technique for improving visualization of mucosal lesions during endoscopic photodynamic therapy. Diagn Ther Endosc 2000;6:147–52.
[11] Moghissi K, Stringer MR, Dixon K. Fluorescence photodiagnosis in clinical practice. Photodiagn Photodyn Ther 2008;5:235–7.

[12] Rimington C. Porphyrin and haem biosynthesis and its control. Acta Med Scand Suppl 1966;445:11–24.
[13] Mayinger B, Reh H, Hochberger J, Hahn EG. Endoscopic photodynamic diagnosis: oral aminolevulinic acid is a marker of GI cancer and dysplastic lesions. Gastrointest Endosc 1999;50:242–6.
[14] Orth K, Russ D, Steiner R, Beger HG. Fluorescence detection of small gastrointestinal tumours: principles, technique, first clinical experience. Langenbeck's Arch Surg/Deutsche Gesellschaft für Chirurgie 2000;385:488–94.
[15] Uedo N, Iishi H, Tatsuta M, Yamada T, Ogiyama H, Imanaka K, et al. A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. Gastrointest Endosc 2005;62:521–8.
[16] Kara MA, Peters FP, Ten Kate FJ, Van Deventer SJ, Fockens P, Bergman JJ. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointest Endosc 2005;61:679–85.
[17] Imaeda H, Hosoe N, Kashiwagi K, Ida Y, Saito Y, Suzuki H, et al. Autofluorescence videoendoscopy system using the SAFE-3000 for assessing superficial gastric neoplasia. J Gastroenterol Hepatol 2010;25:706–11.
[18] Ezoe Y, Muto M, Uedo N, Doyama H, Yao K, Oda I, et al. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. Gastroenterology 2011;141:2017–25, e3.
[19] Osawa H, Yamamoto H, Miura Y, Yoshizawa M, Sunada K, Satoh K, et al. Diagnosis of extent of early gastric cancer using flexible spectral imaging color enhancement. World J Gastrointest Endosc 2012;4:356–61.
[20] Maki S, Yao K, Nagahama T, Beppu T, Hisabe T, Takaki Y, et al. Magnifying endoscopy with narrow-band imaging is useful in the differential diagnosis between low-grade adenoma and early cancer of superficial elevated gastric lesions. Gastric Cancer 2013;16:140–6.
[21] Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, et al. Photodynamic therapy. J Natl Cancer Inst 1998;90:889–905.
[22] Bown SG, Lovat LB. The biology of photodynamic therapy in the gastrointestinal tract. Gastrointest Endosc Clin N Am 2000;10:533–50.
[23] Petersen BT, Chuttani R, Croffie J, DiSario J, Liu J, Mishkin D, et al. Photodynamic therapy for gastrointestinal disease. Gastrointest Endosc 2006;63:927–32.
[24] Mimura S, Ito Y, Nagayo T, Ichii M, Kato H, Sakai H, et al. Cooperative clinical trial of photodynamic therapy with photofrin II and excimer dye laser for early gastric cancer. Lasers Surg Med 1996;19:168–72.
[25] Mimura S, Narahara H, Hirashima T, Fukutomi H, Nakahara A, Kashimura H, et al. Cooperative clinical trial of photodynamic therapy for early gastric cancer with photofrin injection and YAG-OPO laser. Diagn Ther Endosc 1998;4:165–71.
[26] Saragoni L, Morgagni P, Gardini A, Marfisi C, Vittimberga G, Garcea D, et al. Early gastric cancer: diagnosis, staging, and clinical impact. Evaluation of 530 patients. New elements for an updated definition and classification. Gastric Cancer 2013;16:549–54.
[27] Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3–43.
[28] Usuda J, Tsutsui H, Honda H, Ichinose S, Ishizumi T, Hirata T, et al. Photodynamic therapy for lung cancers based on novel photodynamic diagnosis using talaporfin sodium (NPe6) and autofluorescence bronchoscopy. Lung Cancer 2007;58:317–23.