J Med Dent Sci 2018; 65: 27–33

Original Article

Flexible spectral imaging color enhancement markedly reduces the iodine concentration required for the endoscopic diagnosis of superficial esophageal cancer

Chang Ling, Akihiro Hoshino, Yasuaki Nakajima, Kenro Kawada, Yutaka Tokairin, Takuya Okada, Tatsuyuki Kawano and Yusuke Kinugasa

Department of Gastrointestinal Surgery, Tokyo Medical and Dental University

Background: Image-enhanced endoscopy has been increasingly useful for esophageal cancer screening. Although iodine staining is currently the standard modality for the early diagnosis of esophageal cancer, conventionally used concentrations often induce mucosal irritation, leading to discomfort. The aim of the study was to determine the optimal FICE setting and iodine concentration required for maximum color enhancement for the endoscopic diagnosis of superficial esophageal cancer.

Methods: Four esophageal specimens with squamous cell carcinoma that were surgically resected were investigated. The color difference between iodine-stained and background mucosa was evaluated using the 10 preset flexible spectral imaging color enhancement (FICE) wavelength combinations. In addition, the optimum wavelength that best reflected the widest color difference was calculated with and without FICE, and the color differences elicited by different iodine concentrations (from 0.1% to 0.8%) were evaluated with FICE and compared to 1% iodine without FICE (the control).

Results: Maximum color differences were observed using the FICE7 wavelength values. Color enhancement with FICE0, 1, 5 and 7 using a concentration of 0.2% iodine solution or greater was significantly higher than that with the standard 1% iodine concentration ($p < 0.05$).

Conclusions: Low-concentration iodine staining with image-enhanced endoscopy is a useful diagnostic modality that can reduce the degree of discomfort experienced by patients.

Keywords: flexible spectral imaging color enhancement, iodine, endoscopy, gastrointestinal, esophageal cancer.

Corresponding Author: Akihiro Hoshino, M.D.
Department of Gastrointestinal Surgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan
Tel: +81-3-5803-5254 Fax: +81-3-3817-4126
E-mail: hosino.srg1@tmd.ac.jp
Received Octorber 23 ; Accepted December 11, 2017

Introduction

Early detection of esophageal squamous cell carcinoma (ESCC) is essential for achieving a cure[1]. Chromoendoscopy with iodine staining during endoscopy is one of the most effective methods for detecting early ESCC[2]; however, iodine-staining using standard concentrations (1%–3%) has some disadvantages, such as esophageal and gastric mucosal irritation and injury, which can induce chest discomfort and/or coughing as well as possible allergic reactions[3–7]. The aim of this study was to determine the minimum concentration of iodine staining required for esophageal cancer screening with flexible spectral imaging color enhancement (FICE). Although several new image-enhanced endoscopy techniques (including FICE, narrow-band imaging, blue laser imaging, and linked color imaging) have been developed for the detection of early-stage ESCC and assessing the area of cancer spread[8], iodine staining is much more sensitive for detecting flat ESCC and confirming the tumor margin than other techniques and is also easy to learn and apply.

Given the aforementioned side effects, a less-irritating iodine staining method is required. While a low concentration of iodine staining with FICE is clinically feasible (Fig. 1), its merits require proper investigation.

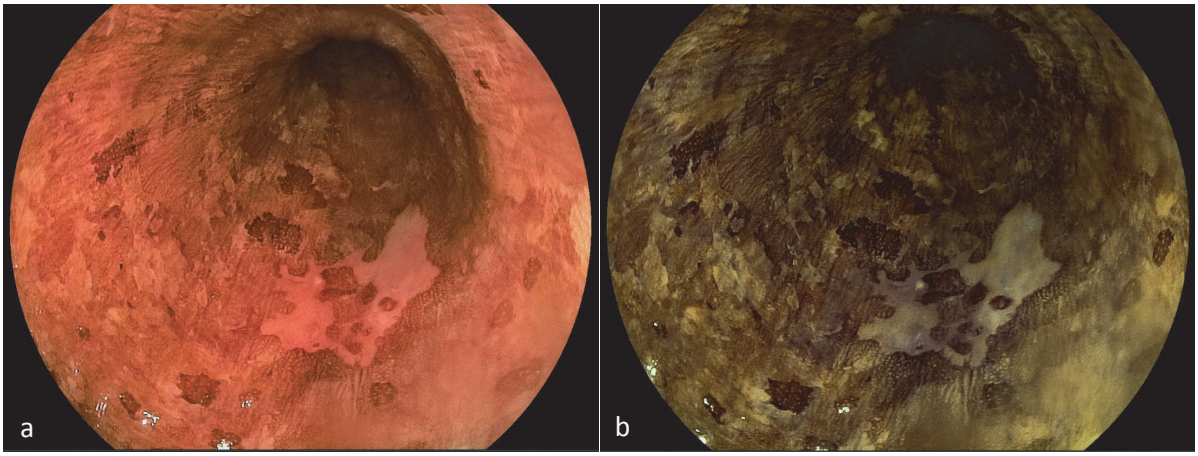

Figure 1. Endoscopic findings using iodine staining without and with FICE.
Endoscopic findings using iodine staining of superficial esophageal cancer without FICE (A) and with FICE (B)

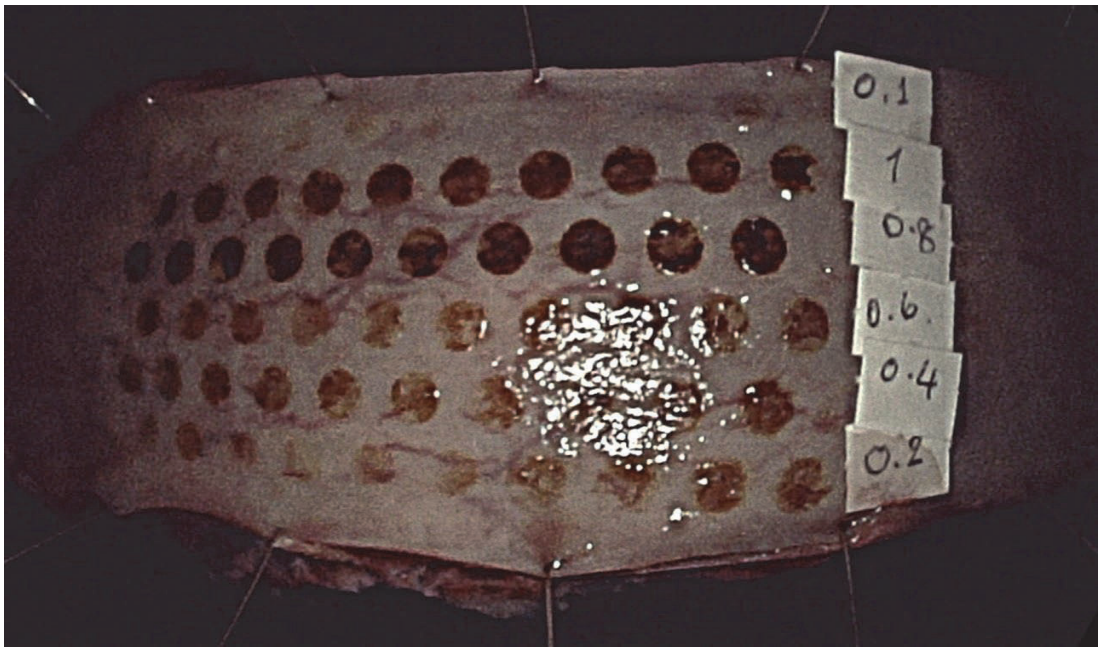

Figure 2. Iodine stainings of different concentrations on an esophageal specimen.
The mucosal surface of an esophageal section 60 s after removing iodine solution. The section was originally exposed to various concentrations of iodine (shown in the right margin [percentages]) using a stainless-steel plate with holes patterned, as evident from the staining. The iodine solution was applied for 30 s before being removed.

Therefore, we compared the effects of FICE with various wavelength settings on the staining of esophageal mucosa to determine the optimum lower concentration of iodine staining for use with FICE.

Materials and Methods

Four consecutive esophageal sections from patients with ESCC that were resected during esophagectomies performed between January 2012 and January 2013 at Tokyo Medical and Dental University were investigated in this study. To assess the stained esophageal normal mucosae with various concentrations of iodine solution, we analyzed a total of 217 stained points across all specimens (i.e. an average of 56 points in each esophageal section). No lesions were observed in the stained area on the specimens microscopically.

First, a stainless steel plate of 10 × 6 cm was affixed to

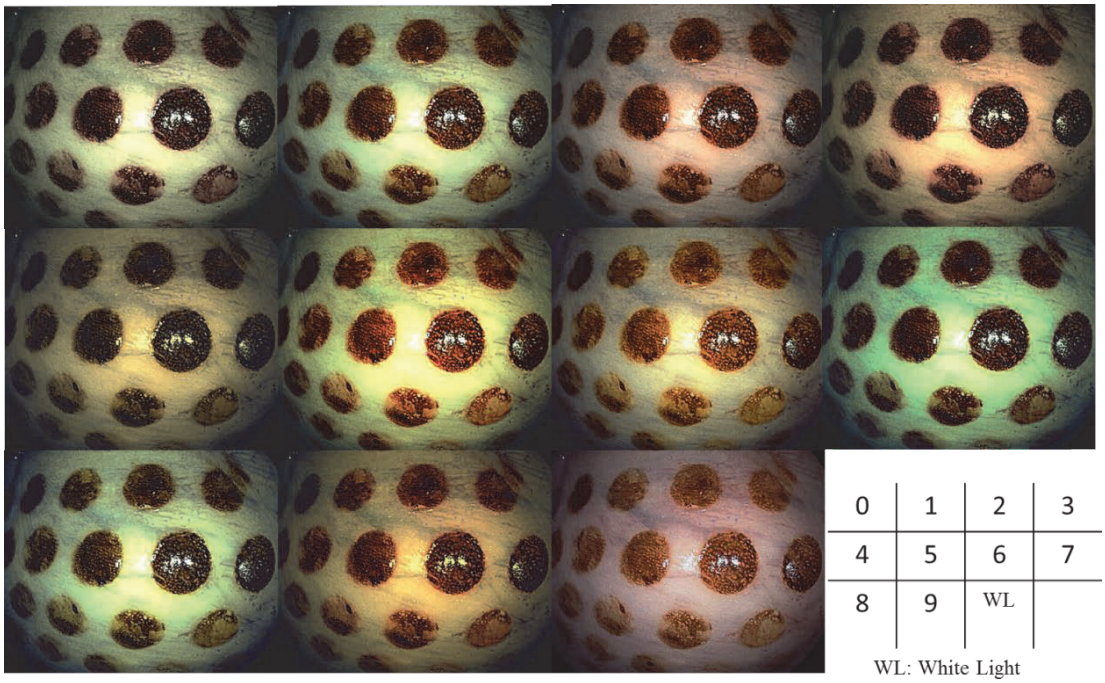

Figure 3. Images with FICE0-9.
Four randomly selected points from stained and unstained esophageal sections were each exposed to various FICE wavelengths, as shown in the legend. The different FICE wavelengths are shown in Table 1.

the resected esophageal specimens. The plate contained 6 × 10 evenly-spaced diameter 6-mm circular holes in the transverse and longitudinal dimensions that were positioned onto the intact mucosal surface of a resected specimen. Iodine solutions of 6 different concentrations (1.0%, 0.8%, 0.6%, 0.4%, 0.2%, and 0.1%) in distilled water were applied to each hole for 30 s before being removed by wiping with gauze. Sixty seconds after removing the iodine solution, the stained surfaces were observed and photographed from a vertical distance of 1 cm from the mucosal surface with a pan-endoscope (EG-590WR; Fuji, Tokyo, Japan) (Fig. 2).

The FICE system, also known as computed virtual chromoendoscopy, was invented by Yoichi Miyake[9-12] and later developed into a commercial product by Fuji Film, Inc. It is a spectral colorimetric endoscopic system for gastrointestinal diagnosis and treatment. This system decomposes images by wavelength, i.e. three single-color images are produced, after which a reconstructed image with enhanced mucosal surface contrast can be generated. Wavelengths of each single-color image can be selected between 400–600 nm in multiples of 5; up to 50 combinations can be selected[13, 14]. The optimal settings and wavelength combinations for FICE are still being determined in clinical practice. Using the FICE system's preset wavelength settings of 0 to 9 (Table 1), segments encompassing stained and unstained areas of the sections were randomly selected, each containing 4 stained points, and the color difference was calculated in CIE 1976 (L*, a*, b*) color space (CIELAB)[15] (Fig. 3 and 4). We calculated the Lab values using the Adobe Photoshop CS4 software program as follows: the rectangle selection tool is used to select the region of interest (ROI), and the histogram of the ROI is displayed. We obtain each Lab value by selecting the Lab of the channel tab in the histogram. The color difference (ΔE) was calculated using the following equation:

$$\Delta E = \sqrt{(L_x - L_y)^2 + (a_x - a_y)^2 + (b_x - b_y)^2}$$

where x = the stained part and y = the unstained part, L = lightness, a = the red-green component, and b = the yellow-blue component.

The color differences between the photographs of the stained and unstained areas in each section were calculated for the FICE0-9 system's wavelength setting. First, the optimum wavelength mode in FICE0-9 was determined by calculating the increasing rate (ΔR) of the color differences (ΔE) for all iodine concentrations except for 1%, per the following equation:

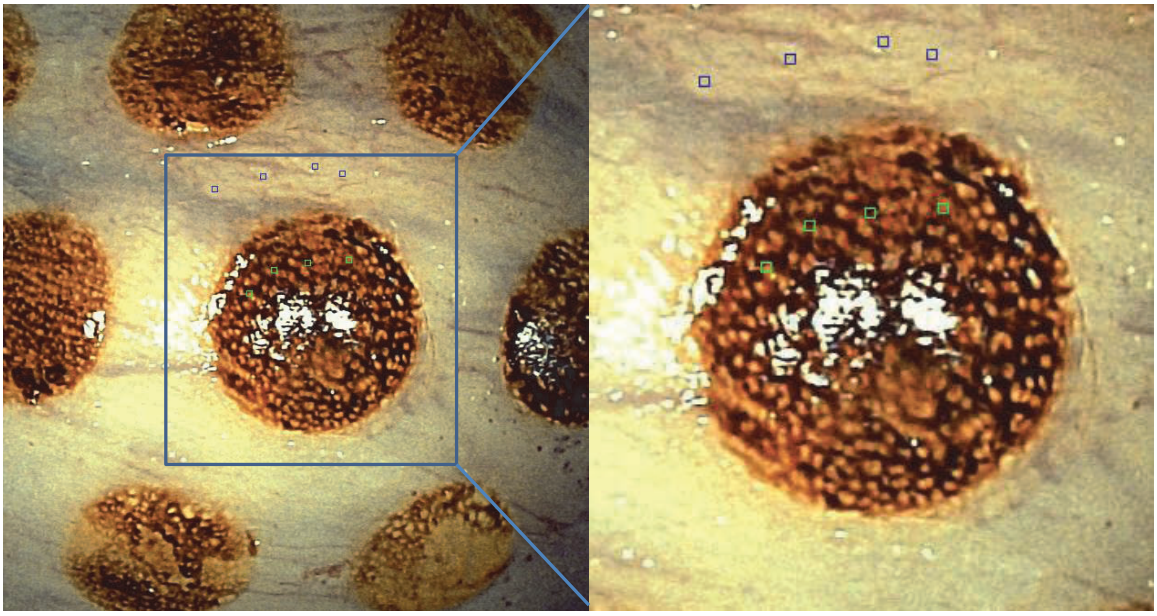

Figure 4. The method of calculating the color differences.
The differences in color between the stained area (green squares) and the unstained area (blue squares) were calculated in CIE 1976 (L*, a*, b*) color space (CIELAB).[15]

Table 1. The preset FICE wavelength combinations (nm)

	Red	Green	Blue
FICE0	525	495	495
FICE1	550	500	470
FICE2	550	500	470
FICE3	525	495	495
FICE4	520	500	405
FICE5	560	500	475
FICE6	580	520	460
FICE7	540	490	420
FICE8	540	505	420
FICE9	550	500	400

$$\Delta R = \frac{c}{d}$$

where c = the color difference (ΔE) with FICE, d = the color difference (ΔE) without FICE.

Next, the concentration of the iodine solution that produced the greatest color difference using FICE when compared to the unstained mucosa was determined; the 1% concentration iodine solution without FICE was used as a control.

This study was approved by the Ethics Committee of Tokyo Medical and Dental University (approval number M2000-2300). Statistical analyses were performed using the JMP software program, version 10.0.0 (SAS Institute Inc., Cary, NC, USA). Dunnett's test was used to compare the average data of each concentration with FICE to the control group for statistical analyses; $p < 0.05$ was judged to be significantly different.

Results

Of the 217 sites stained with various concentrations of iodine solution, 183 were evaluated in the study; 34 sites with incomplete iodine staining owing to either the presence of many small unstained areas or multiple carcinomas were excluded. The evaluable sites included 27 with iodine solution concentrations of 1.0%, 29 with concentrations of 0.8%, 34 with concentrations of 0.6%, 35 with concentrations of 0.4%, 34 with concentrations of 0.2%, and 24 with concentrations of 0.1%. The average difference in the increasing rate (ΔR) with FICE enhancement was highest when using FICE7, and the second-highest was when using FICE5. (Table 2). An iodine concentration of 0.2% or higher using FICE0, 1, 5, and 7 showed a significantly higher average color difference (ΔE) than a concentration of 1.0% without FICE ($p < 0.05$) (Table 3 and Fig. 5).

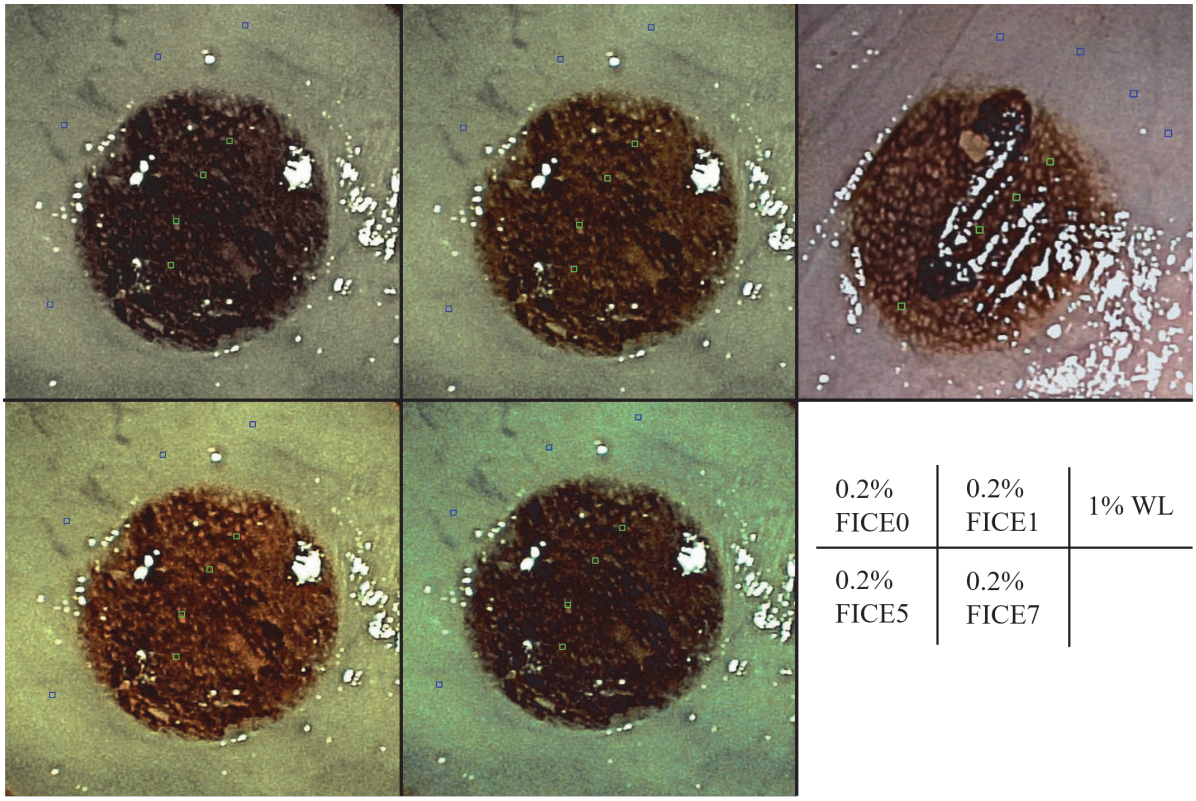

Figure 5. Images of 0.2% iodine staining with FICE0, 1, 5, and 7 compared with the control (1% without FICE). These images of 0.2% iodine staining with FICE0, 1, 5, and 7 that showed significantly higher color differences than the control.

Table 2. The increasing rate (ΔR) of the color difference with FICE

	Concentration					
	0.80% (n = 29)	0.60% (n = 34)	0.40% (n = 35)	0.20% (n = 34)	0.10% (n = 24)	All (n = 156)
FICE0	1.60 (1.45–1.82)	1.55 (1.25–1.81)	1.57 (1.18–1.75)	1.59 (0.97–1.83)	1.08 (0.68–1.76)	1.52 (0.68–1.83)
FICE1	1.66 (1.49–1.84)	1.63 (1.40–1.83)	1.65 (1.40–1.79)	1.67 (1.28–1.83)	1.32 (1.00–1.79)	1.61 (1.00–1.84)
FICE2	1.23 (1.13–1.37)	1.22 (0.61–1.34)	1.24 (1.09–1.47)	1.24 (1.09–1.37)	1.31 (1.06–1.36)	1.24 (0.61–1.47)
FICE3	1.49 (1.28–1.68)	1.39 (1.07–1.64)	1.39 (0.99–1.58)	1.39 (0.90–1.69)	1.08 (0.65–1.62)	1.36 (0.65–1.69)
FICE4	1.36 (1.13–1.57)	1.23 (0.81–1.50)	1.23 (0.72–1.50)	1.23 (0.60–1.52)	0.79 (0.37–1.40)	1.19 (0.37–1.57)
FICE5	1.95 (1.80–2.12)	1.92 (1.70–2.20)	1.93 (1.70–2.09)	1.92 (1.47–2.19)	1.64 (1.09–2.11)	1.89 (1.09–2.20)
FICE6	1.33 (1.21–1.56)	1.31 (1.19–1.41)	1.29 (1.21–1.39)	1.28 (1.20–1.48)	1.44 (1.24–1.60)	1.31 (1.19–1.60)
FICE7	1.97 (1.74–2.26)	1.97 (1.30–2.32)	2.03 (1.71–2.32)	2.07 (1.48–2.31)	1.54 (0.86–2.37)	1.97 (0.86–2.37)
FICE8	1.73 (1.49–2.03)	1.60 (1.16–1.91)	1.60 (1.14–1.87)	1.60 (1.02–1.93)	1.22 (0.84–1.78)	1.56 (0.84–2.03)
FICE9	1.39 (1.18–1.61)	1.30 (1.08–1.51)	1.28 (1.10–1.48)	1.28 (1.01–1.56)	1.22 (0.86–1.38)	1.28 (0.86–1.61)

Values are expressed as the mean (range).

Table 3. A comparison of the color differences between the control and each low concentration with FICE0-9

	low concentration					control
	0.8%	0.6%	0.4%	0.2%	0.1%	1%
FICE0	71.5±13.8*	61.1±13.3*	59.2±12.4*	56.9±15.4*	28.9±17.5*	46.7±6.1
FICE1	73.9±14.1*	64.1±12.8*	62.0±12.1*	59.4±14.9*	31.9±16.5*	
FICE2	55.0±10.5*	47.7±9.8	46.6±7.8	44.8±9.7	27.2±10.2*	
FICE3	66.5±13.6*	55.0±13.6*	52.8±12.4	48.1±12.4	26.0±14.6*	
FICE4	60.9±13.3*	48.8±13.7	46.8±12.9	42.9±13.5	20.9±14.0*	
FICE5	86.7±15.5*	75.2±14.2*	72.7±13.2*	69.0±16.1*	38.0±18.6	
FICE6	59.3±12.1*	51.2±10.0	48.7±9.3	45.8±9.8	28.8±9.3*	
FICE7	87.7±16.3*	77.2±15.6*	76.2±13.4*	74.4±18.4*	39.5±22.0	
FICE8	77.4±16.3*	63.4±16.5*	60.8±15.2*	56.1±16.3	29.0±16.4*	
FICE9	62.3±13.6*	51.4±12.4	48.5±10.9	44.8±11.0	25.5±11.5*	

Values are expressed as the mean± standard deviation
* Significant difference from the control ($p < 0.05$)

Discussion

In this study, we calculated the incremental differences in iodine color contrasts when using FICE to examine esophageal cancer and concluded that a wavelength combination of R = 540 nm, G = 490 nm, and B = 420 nm (the 7th preset; FICE7) best suits this application, although the increasing rate of FICE5 was similar to that of FICE7. In addition, we found that the minimum iodine concentration that produces a contrast under FICE0, 1, 5, and 7 and was similar to that of conventional 1% iodine staining without FICE was 0.2%.

Osawa et al.[16] reported that FICE was able to enhance the color difference between Barret esophageal mucosa and paliform blood vessels and showed that vascular markings could be observed clearly by FICE. However, they did not describe the optimum wavelength of the FICE endoscope. Corita et al.[13] used FICE to systemically observe gastrointestinal polyps and proposed that the fourth combination of wavelengths (R = 520 nm, G = 500 nm, and B = 405 nm) was the best. Pohl et al.[14] compared FICE to the indigo carmine dying method and observed pits and vascular markings in mucosae using the blue-band wavelength combinations; they found that the best result was obtained with the combination of the following 3 wavelengths: R = 500 nm, G = 480 nm, and B = 420 nm. However, they only presented a subjective assessment and comparison of different wavelength combinations in terms of the visibility of blood vessels in scar tissue. In our study, the optimum wavelength of FICE with iodine staining of esophageal lesions was determined to be R = 540 nm, G = 490 nm, and B = 420 nm.

Chromoendoscopy is a medical procedure in which dyes are instilled onto the mucosa at the time of visualization with endoscopy in order to derive diagnostic information from the contrast between the normal tissue and the lesion. Iodine-staining chromoendoscopy can significantly improve the detection rate for early esophageal cancer and pre-cancerous lesions[2, 17]. However, conventional iodine staining often causes a retrosternal burning sensation, discomfort, and other adverse reactions, even if the patient has no erosion or ulceration in the esophageal mucosa[18, 19]. In this study, a 0.2% concentration of iodine with FICE7 resulted in a contrast equal to or higher than the conventionally used 1%. To our knowledge, this is the first study to report the efficacy of lower concentrations of iodine, although Kondo et al. reported that the side effects of iodine staining were significantly reduced by using sodium thiosulfate solution spray[19].

The limitation of this study was that it was performed on resected tissues, not endogenous samples. The efficacy of low-concentration iodine staining with FICE in clinical practice should be considered in future studies.

In conclusion, it is possible to perform low-concentration iodine staining with FICE. This method can lead to reduced discomfort in patients and may have the potential to be widely applied to esophageal cancer screening.

References

1. Yoshida Y, Goda K, Tajiri H, et al. Assessment of novel endoscopic techniques for visualizing superficial esophageal squamous cell carcinoma: autofluorescence and narrow-band imaging. Dis Esophagus. 2009;22:439-46.
2. Shiozaki H, Tahara H, Kobauashi K, et al. Endoscopic screening of early esophageal cancer with the lugol dye method in patients with head and neck cancers. Cancer. 1990;66:2068-71.
3. Shimizu Y, Tukagoshi H, Fujita M, et al. Endoscopic screening for early esophageal cancer by iodine staining in patients with other current or prior primary cancers. Gastrointest Endosc. 2001;53:1-5.
4. Park J, Lee I, Young Kang J, et al. Acute esophageal and gastric injury: complication of Lugol's solution. Scand J Gastroenterol. 2007;42:135-7.
5. Thuler FP, de Paulo GA, Ferrari AP. Chemical esophagitis after chromoendoscopy with Lugol's solution for esophageal cancer: case report. Gastrointest Endosc. 2004;59:925-6.
6. Sreedharan A, Rembacken BJ, Rotimi O. Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy. Gut. 2005;54:886-7.
7. Tsurumaru D, Utsunomiya T, Matsuura S, et al. Gastric mucosal changes caused by lugol's iodine solution spray: endoscopic features of 64 cases on screening esophagogastroduodenoscopy. Gastroenterol Res Pract. 2010; doi: 10.1155/2010/494195.
8. Nagami Y, Tominaga K, Machida H, et al. Usefulness of non-magnifying narrow-band imaging in screening of early esophageal squamous cell carcinoma: a prospective comparative study using propensity score matching. Am J Gastroenterol. 2014;109:845-54.
9. Miyake Y, Sekiya T, Kubo S, et al. A new spectrophotometer for measuring the spectral reflectance of gastric mucous membrane. J Photogr Sci. 1989;37:134-8.
10. Shiobara T, Zhou S, Haneishi H, et al. Improved color reproduction of electronic endoscopes. J Imag Sci Technol. 1996;40:494-501.
11. Tsumura N, Tanaka T, Haneishi H, et al. Optimal design of mosaic color electronic endoscopes. Opt Commun. 1998;145:27-32.
12. Shiobara T, Haneishi H, Miyake Y. Color correction for colorimetric color reproduction in an electronic endoscope. Opt Commun. 1995;114:57-63.
13. Coriat R, Chryssostalis A, Zeitoun JD, et al. Computed virtual chromoendoscopy system (FICE): a new tool for upper endoscopy? Gastroenterol Clin Biol. 2008;32:363-9.
14. Pohl J, May A, Rabenstein T, et al. Computed virtual chromoendoscopy (CVC): a new tool for enhancing tissue surface structures. Endoscopy. 2007;39:80-3.
15. Kuehni RG. Color-tolerance data and the tentative CIE 1976 L*a*b* formula. J Opt Soc Am. 1976;66:497-500.
16. Osawa H, Yamamoto H, Yamada N, et al. Diagnosis of endoscopic Barrett's esophagus by transnasal flexible spectral imaging color enhancement. J Gastroenterol. 2009;44:1125-32.
17. Pech O, May A, Gossner L, et al. Curative endoscopic therapy in patients with early esophageal squamous-cell carcinoma or highgrade intraepithelial neoplasia. Endoscopy. 2007;39:30-5.
18. Curvers WL, Kiesslich R, Bergman JJ. Novel imaging modalities in the detection of oesophageal neoplasia. Best Pract Res Clin Gastroenterol. 2008;22:687-720.
19. Kondo H, Fukuda H, Ono H, et al. Sodium thiosulfate solution spray for relief of irritation caused by Lugol's stain in chromoendoscopy. Gastrointest Endosc. 2001;53:199-202.