ORIGINAL PAPER

The utility of ultrathin endoscopy with flexible spectral imaging color enhancement for early gastric cancer

Takafumi Yokoyama[1], Ryoji Miyahara[1], Kohei Funasaka[1], Kazuhiro Furukawa[2],
Takeshi Yamamura[1], Eizaburo Ohno[2], Masanao Nakamura[1], Hiroki Kawashima[1],
Osamu Watanabe[1], Yoshiki Hirooka[2], Akihiro Hirakawa[3], and Hidemi Goto[1]

[1]Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine,
Nagoya, Japan
[2]Department of Endoscopy, Nagoya University Hospital, Nagoya Japan
[3]Biostatistics Section, Center for Advanced Medicine and Clinical Research, Nagoya University Graduate
School of Medicine, Nagoya Japan

ABSTRACT

Many researchers suggested that ultrathin endoscopy improves patient acceptance of endoscopic examinations. However, ultrathin endoscopy provides less image resolution and luminous intensity. Therefore, we focused on the visibility of early gastric cancer on ultrathin endoscopy with Flexible spectral imaging color enhancement (FICE) in this study. Thirty-six patients with early gastric cancer were prospectively enrolled. One endoscopist performed the endoscopic examinations by white light conventional endoscopy (W-CE), white light ultrathin endoscopy (W-UE), FICE ultrathin endoscopy (F-UE) and white light plus FICE ultrathin endoscopy (WF-UE) in the patients. Four other endoscopists were asked to evaluate the visibility of gastric cancer on the W-CE, W-UE, F-UE and WF-UE images with a 5-point Likert scale. The lesions were classified as uncolored, normocolored or reddish. We examined the color difference between early gastric cancer and the surrounding mucosa. To examine the relationship between the color difference and the vessel density, we also measured the difference in vessel density using pathologic specimens stained with hematoxylin and eosin. The Likert score of WF-UE was significantly higher than those of the other three methods ($p<0.001$). The color difference of F-UE was higher than that of W-CE in the reddish group ($p=0.049$). The difference in vessel density was higher in the reddish group than in the normocolored group ($p=0.048$). In conclusion, the visibility of early gastric cancer from the surrounding mucosa using ultrathin endoscopy with FICE was better than that using white light conventional endoscopy, especially for reddish lesions.

Keywords: ultrathin endoscopy, early gastric cancer, flexible spectral imaging color enhancement, color difference

INTRODUCTION

Recently, endoscopic treatments such as endoscopic submucosal dissection (ESD) and endo-

scopic mucosal resection (EMR) have enabled us to curatively resect a portion of early gastric cancers.[1] They have improved the quality of life of patients because the function of the stomach can be kept completely. It is important to detect early gastric cancer so that it can be treated endoscopically.

Ultrathin endoscopy has been used mainly for gastric cancer screening since this method was invented in Japan. Many reports suggested that ultrathin endoscopy improves patient acceptance of endoscopic examinations in the absence of sedation and lowers the total cost of endoscopic examination compared with conventional endoscopy with sedation.[2,3] However, ultrathin endoscopy provides less image resolution and luminous intensity. Therefore, the ability of ultrathin endoscopy to detect early gastric cancer may not be satisfactory.

Image-enhanced endoscopy (IEE) was developed to improve the diagnostic accuracy of gastrointestinal cancer. IEE consists of the use of digital, optical or chromoendoscopic methods to enhance differences in contrast between the carcinoma and the surrounding mucosa. Flexible spectral imaging color enhancement (FICE) is one of the IEE methods.[4] White light consists of light wavelengths of seven colors, and FICE captures images by each wavelength and reconstitutes virtual images according to the choice of different combinations of wavelengths. The FICE system provides high-contrast images with the same light intensity as white light images.

Therefore, we examined the hypothesis that the FICE system may compensate the disadvantages of ultrathin endoscopy such as less image resolution and luminous intensity. In this study, we focused on the visibility of early gastric cancer on ultrathin endoscopic images with FICE.

MATERIALS AND METHODS

This study included patients with early gastric cancer in whom we planned to perform ESD at Nagoya University Hospital in Nagoya, Japan between April 2013 and May 2014. Early gastric cancer was diagnosed by histological examination of biopsy specimens of the gastric lesion. The exclusion criterion was lack of patient's consent. A total of 77 patients with early gastric cancer underwent ESD during the study period. Of these, 36 patients were prospectively enrolled in the present study. White light images and FICE images of ultrathin endoscopy and white light images of conventional endoscopy were obtained. This study was approved by the Institutional Review Board of our institution, and is registered in the UMIN database (UMIN:000017982). Written informed consent was obtained from each patient before endoscopy. The lesions consisted of 35 early differentiated adenocarcinomas and 1 early undifferentiated adenocarcinoma. Ultrathin endoscopy was performed with the EG-580NW endoscope (end diameter 5.9 mm: FUJIFILM Corporation, Saitama, Japan), and conventional endoscopy was performed with the EG-590WR2 endoscope (end diameter 10.8 mm: FUJIFILM Corporation). The FICE system has a set of wavelengths including 495nm for blue(B), 495nm for green(G) and 525nm for red(R).

Before ESD, the lesion was observed by conventional endoscopy and by ultrathin endoscopy. One endoscopist obtained endoscopic images by white light conventional endoscopy (W-CE), white light ultrathin endoscopy (W-UE), FICE ultrathin endoscopy (F-UE) and white light plus FICE ultrathin endoscopy (WF-UE) from each patient. Afterwards, four endoscopists who were not informed about the cancers, were asked to evaluate the visibility of the lesions in the W-CE, W-UE, F-UE and WF-UE images of each patient by a 5-point Likert scale (Figure 1). Image quality was graded on the Likert scale as follows: grade 5, "very well", it is easy to point out the lesion and there is a clear border at the circumference of the lesion; grade 4, "well", it is easy to point out the lesion with a somewhat clear border at the circumference of the lesion; grade 3, "average", it is easy to point out the lesion; grade 2, "poor", it is difficult to point out
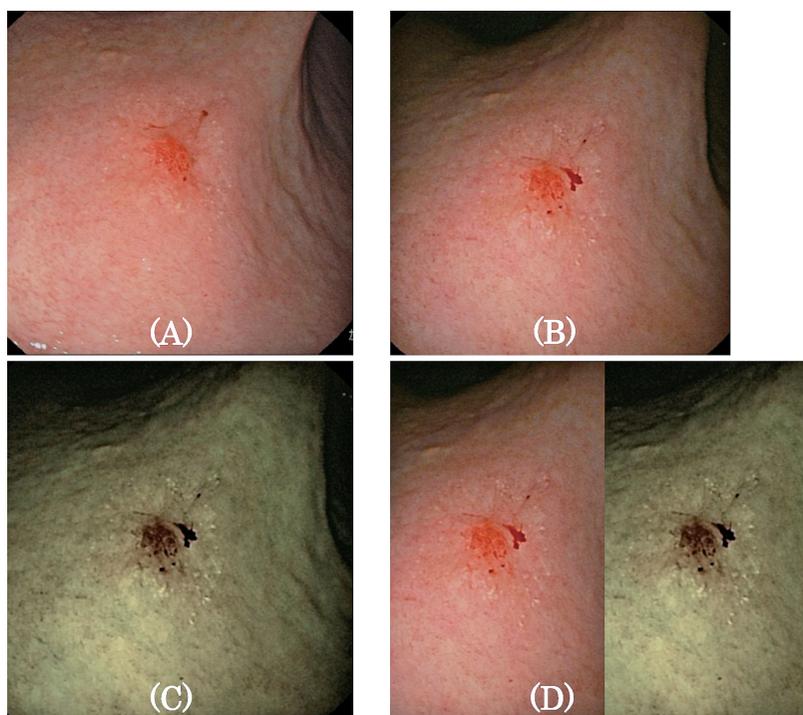
Fig. 1 Representative views on images of each endoscopy.
Representative views of early gastric cancer in a patient on images of (A) white light conventional endoscopy (W-CE), (B) white light ultrathin endoscopy (W-UE), (C) FICE ultrathin endoscopy (F-UE), and (D) white light plus FICE ultrathin endoscopy (WF-UE)

the lesion; and grade 1, "very poor", the endoscopist failed to point out the lesion. Two of the four endoscopists were certified members of the Japanese Gastroenterological Endoscopy Society.

The CIE1976(L a b) color space was used to calculate color differences.[5,6] The CIE1976(L a b) system is one of the color space models, and is similar to human color perception. In this system, "L" is defined as lightness, "a" is the red-green component, and "b" is the yellow-blue component. When two different colors are compared, each color is located in the CIE1976(L a b) color space and the length between them is measured. The length is referred to as "the color difference." Two suitable points each were selected at random from the cancer and from the surrounding mucosa. Then, we measured 4 color differences between the 2 points in the cancer and the 2 points in the surrounding mucosa, and calculated the mean of the color differences.

The relationship between the color difference in the endoscopic image and the area of vascular space in the resected specimens that had been subjected to pathological examination, was examined.[7] To measure the area of the vascular space, pathological specimens stained with hematoxylin and eosin were used. We observed the center of the cancer and the surrounding mucosa in each specimen at ×100 magnification and identified vessels with cellSens (Olympus Co. Ltd., Tokyo, Japan). We calculated the difference in vessel density by subtracting the vessel density in the surrounding mucosa from that in the cancer. To investigate the color differences in detail, one endoscopist classified the gastric cancers according to the color of the gastric cancer on WF-UE images into the reddish group (14 cases), normocolored group (13 cases) and uncolored group (9 cases) on observation.

For each endoscopist, we determined and compared the proportion of cancers that were rated as grade 4 or 5 in each of the 4 methods (W-CE, W-UE, F-UE, WF-UE) and combined the difference in proportion with grades 4 and 5 among the 4 methods based on the 4 endoscopists using the meta-analysis approach. We also evaluated the consistency (i.e., kappa coefficient) between an arbitrary 2 methods and conducted McNemar's test. Analysis of variance followed by Tukey's multiple comparison methods was used to evaluate color difference and the difference in vessel density. A two-sided $p < 0.05$ was considered to be statistically significant. These statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, US) and SPSS version 23 (SPSS Japan Inc., Tokyo, Japan).

RESULTS

The baseline characteristics of the 36 patients are shown in Table 1. The proportions of patients with each endoscopic image score are shown in Table 2. We divided the patients into two groups of those with grade 4, 5 and those with grade 1,2,3 in each method. The proportion of patients with grade 4,5 by WF-UE was significantly higher than that by W-UE, W-CE or F-UE (Figure 2). The kappa coefficients were between 0.019 and 0.77.

We compared the color difference between the cancer and the surrounding mucosa on the W-CE, W-UE, and F-UE images among all cases, among the reddish cases, among the uncolored cases, and among the normocolored cases. Among all cases, the color difference on F-UE was not significantly higher than that on W-CE (F-UE:21.92±11.68 W-CE:20.38±7.69 P=0.762). In the reddish group, the color difference on F-UE was significantly higher than that on W-CE (F-UE:29.11±11.58 W-CE:22.57±8.50 P=0.049).

We investigated the density of blood vessels in the color groups. The difference in vessel density in the surrounding mucosa from that in the cancer was 0.0297±0.0483 (mean±SD) in the uncolored group, 0.0210±0.0328 in the normocolored group, and 0.0899±0.1045 in the reddish group. The difference in vessel density was significantly higher in the reddish group than in the

Table 1 Characteristics of the 36 patients with early gastric cancer

|	
Age (year) (median, range)	70 (57–82)
Sex (M/F)	26 / 10
Macroscopic type	0–Ⅱa : 10 0–Ⅱa+Ⅱc : 4 0–Ⅱc : 22
Tumor differentiation	differentiated : 35 undifferentiated : 1
Tumor depth	M : 32 SM : 4
Tumor size (mm) (median, range)	15 (4–63)
Tumor color group	reddish : 14 uncolored : 13 normocolored : 9

normocolored group (*P*=0.048).

Table 2–1 Comparison of the score ratings of each of the 4 endosopists in every combination by the difference in the proportion of ratings of 4 or 5 and consistency

Dr.A	1	2	3	4	5		W-UE	F-UE	WF-UE
W-CE	0(0.0)	3(8)	28(78)	4(11)	1(3)	The difference of 4 and 5 proportion to W-CE(95%CI)	0 (−8, 8)	39 (23, 55)	39 (23, 55)
W-UE	0(0.0)	15(42)	16(44)	3(8)	2(6)	McNemar's probability	1.000	0.0002	0.0002
F-UE	0(0.0)	2(6)	15(42)	17(47)	2(6)	K coefficient	0.77	0.25	0.25
WF-UE	0(0.0)	2(6)	15(42)	17(47)	2(6)				
Dr.B									
W-CE	0(0.0)	4(11)	15(42)	16(44)	1(3)	The difference of 4 and 5 proportion to W-CE(95%CI)	−25 (−39, −11)	−31 (−51, −10)	3 (−15, 21)
W-UE	1(3)	5(14)	22(61)	7(19)	1(3)	McNemar's probability	0.003	0.0076	0.763
F-UE	2(6)	4(11)	24(67)	5(14)	1(3)	K coefficient	0.48	0.019	0.3889
WF-UE	0(0.0)	3(8)	15(42)	17(47)	1(3)				
Dr.C									
W-CE	0(0.0)	4(11)	24(67)	7(19)	1(3)	The difference of 4 and 5 proportion to W-CE(95%CI)	−8 (−17, 1)	2 (9, 36)	44 (28, 61)
W-UE	0(0.0)	8(22)	23(64)	4(11)	1(3)	McNemar's probability	0.083	0.0047	<.0001
F-UE	0(0.0)	2(6)	18(50)	13(36)	3(8)	K coefficient	0.72	0.53	0.25
WF-UE	0(0.0)	0(0.0)	12(33)	20(56)	4(11)				
Dr.D									
W-CE	0(0.0)	3(8)	10(28)	19(53)	4(11)	The difference of 4 and 5 proportion to W-CE(95%CI)	−33 (−49, −18)	3 (−12, 17)	3 (−12, 17)
W-UE	0(0.0)	4(11)	21(58)	9(25)	2(6)	McNemar's probability	0.0005	0.7055	0.7055
F-UE	0(0.0)	2(6)	10(28)	20(56)	4(11)	K coefficient	0.398	0.57	0.57
WF-UE	0(0.0)	2(6)	10(28)	20(56)	4(11)				
						The difference of 4 and 5 proportion to W-CE(95%CI)	−9.7 (−15.0, −4.5)	12.2 (4.6, 19.8)	21.8 (14.1, 29.5)
						probability	0.0003	0.0017	< 0.0001

Takafumi Yokoyama et al

Table 2–2 Comparison of the score ratings of each of the 4 endosopists in every combination by the difference in the proportion of ratings of 4 or 5 and consistency

	F-UE	WF-UE		WF-UE
The difference of 4 and 5 proportion to W-UE(95%CI)	39 (23, 55)	39 (23, 55)	The difference of 4 and 5 proportion to F-UE(95%CI)	0 (0, 0)
McNemar's probability	0.0002	0.0002	McNemar's probability	n/a
K coefficient	0.25	0.25	K coefficient	1
The difference of 4 and 5 proportion to W-UE(95%CI)	–6 (–21, 10)	28 (13, 42)	The difference of 4 and 5 proportion to F-UE(95%CI)	33 (18, 49)
McNemar's probability	0.4795	0.0016	McNemar's probability	0.0005
K coefficient	0.2941	0.4444	K coefficient	0.333
The difference of 4 and 5 proportion to W-UE(95%CI)	31 (16, 46)	53 (36, 69)	The difference of 4 and 5 proportion to F-UE(95%CI)	22 (9, 36)
McNemar's probability	0.0009	0.0047	McNemar's probability	0.0047
K coefficient	0.34	0.57	K coefficient	0.57
The difference of 4 and 5 proportion to W-UE(95%CI)	36 (20, 52)	36 (20, 52)	The difference of 4 and 5 proportion to F-UE(95%CI)	0 (0, 0)
McNemar's probability	0.0003	0.0003	McNemar's probability	n/a
K coefficient	0.36	0.36	K coefficient	1
The difference of 4 and 5 proportion to W-UE(95%CI)	25.0 (17.2, 32.8)	38.2 (30.7, 45.8)	The difference of 4 and 5 proportion to F-UE(95%CI)	26.8 (16.4, 37.1)
probability	< 0.0001	< 0.0001	probability	<0.0001
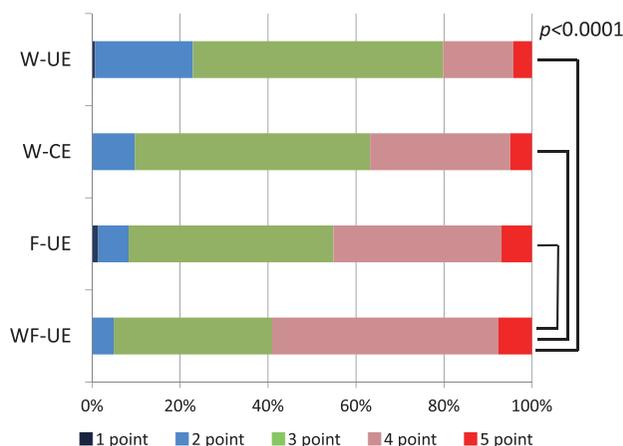
Fig. 2 The proportion of lesions rates of each endoscopy.
Visibility of lesions on images of white light ultrathin endoscopy (W-UE), white light conventional endoscopy (W-CE), FICE ultrathin endoscopy (F-UE), and white light plus FICE ultrathin endoscopy (WF-UE). Four endoscopists were asked to rate the visibility of lesions on a 5-point Likert scale. The proportion of lesions rated as grade 4 or 5 was significantly higher in the WF-UE images than in the other images.

DISCUSSION

Several studies reported that ultrathin endoscopy was associated with a shorter recovery time and lower cost of examination compared with conventional endoscopy under sedation. However, only a few studies have compared ultrathin endoscopy with conventional endoscopy in terms of detectability of early gastric cancer.[8-10] Some reports suggested that the diagnostic utility of ultrathin endoscopy might be lower than that of conventional endoscopy.[11-13] The reports that demonstrated the lower utility of ultrathin endoscopy insisted that ultrathin endoscopy requires additional procedures to enhance visualization such as close-range observation and chromoendoscopy.[14] Therefore, we compared the visibility of lesions under ultrathin endoscopy with FICE which compensates for the disadvantage of low-resolution images and low light intensity, with that under conventional endoscopy. In this study, the score on WF-UE was significantly superior to the scores on the other methods. This result may suggest that FICE compensates for the disadvantages of ultrathin endoscopy.

Although the color difference between the cancer and the surrounding mucosa among all cases did not show a significant difference, the color difference on FICE ultrathin endoscopic images was significantly higher than that on W-CE images in reddish early gastric cancer cases. Therefore, FICE may be suitable for reddish lesions. We thought that the higher color difference in the reddish group was due to vessel density. We calculated the difference in vessel density between the cancer and the surrounding mucosa, and the difference in the reddish group was higher than that in the other groups. The result may suggest one of the reasons that the color difference on F-UE was higher than that on W-CE in reddish lesions. It was confirmed that the reddish early gastric cancers had many vessels which contain red blood cells, suggesting that the reddish early gastric cancers are more likely to flourish.

Limitations of the present study were that it was a single-center study with a small number of cases and this study was not powered for analysis of the scores of the reddish, normocolored and uncolored groups. We didn't evaluate the white light plus FICE conventional endoscopy

(WF-CE), too. We feel that further investigation of detectability of early gastric cancer by ultrathin endoscopy is necessary.

In conclusion, the visibility of early gastric cancer from the surrounding mucosa using ultrathin endoscopy with FICE was better than that using white light conventional endoscopy, especially for reddish lesions.

CONFLICT OF INTEREST

No potential conflict of interest are disclosed.

REFERENCES

1. Junbi Hu, Yan Zhao, Mudan Ren, et al. The comparison between endoscopic submucosal dissection and surgery in gastric cancer: a systematic review and meta-analysis. *Gastroenterology Reseach and Practice*. 2018;2018:4378945.
2. Gracia RT, Cello JP, Nguyen MH, Rogers SJ, Rodas A, Trinh HN. Unsedated ultrathi EGD is well accepted compared with conventional sedated EGD: a multicenter randomized trial. *Gastroenterology*. 2003;125:1606–1612.
3. Preiss C, Charton JP, Schumacher B, Neuhaus H. A randomized trial of unsedated transnasal small-caliber esophagogastroduodenoscopy (EGD) versus peroral small-caliber EGD versus conventional EGD. *Endoscopy*. 2003;35:641–645.
4. Osawa H, Yamamoto H, Miura Y, et al. Diagnosis of extetnt of early gastric cancer using Flexible spectral imaging color enhancement. *World J Gastrointest Endosco*. 2012;16:356–361.
5. Osawa H, Yamamoto H, Miura Y, et al. Diagnosis of depressed-type early gastric cancer using small-caliber endoscopy with flexible spectral imaging color enhancement. *Digestive Endoscopy*. 2012;24:231–236.
6. Osawa H, Yamamoto H, Miura Y, et al. Diagnosis of depressed-type early gastric cancer using small-caliber endoscopy with flexible spectral imaging color enhancement. *Digestive Endoscopy*. 2012;24:231–236.
7. Mouri R, Yoshida S, Tanaka S, Oka S, Yoshihara M, Chayama K. Evaluation and validation of computed virtual chromoendoscopy in early gastric cancer. *Gastrointestinal Endoscopy*. 2009;69:1052–1058.
8. Hayashi Y, Yamamoto Y, Suganuma T, et al. Comparison of the diagnostic utility of the ultrathin endoscopy and the conventional endoscope in early gastric cancer screening. *Digestive Endoscopy*. 2009;21:116–121.
9. Nakata H, Enomoto S, Maekita T, et al. Transnasal and standard transoral endoscopies in the screening of gastric mucosal neoplasias. *World J Gastrointest Endosc*. 2011;3:162–170.
10. Osawa H, Yoshizawa M, Yamamoto H, et al. Optimal band imaging system can facilitate detection of changes in deppressed-type early gastric cancer. *Gasstrointest Endosc*. 2008;67:226–234.
11. Nakamura M, Nishikawa J, Goto A, et al. Usefulness of ultraslim endoscopy with flexible spectral imaging color enhancement for detection of gastric neoplasm: a preliminary study. *J Gastrointest Canc*. 2013;44:325–328.
12. Yukari T, Hideo Y, Eiki S. Ultraslim endoscopy with flexible spectral imaging color enhancement for upper gastrointestinal neoplasms. *World J Gastrointest Endosc*. 2011;3:11–15.
13. Birkner B, Fritz N, Schatke W, Hasford J. A prospective randomized comparison of unsedated ultrathin versus standard esophagogastroduodenoscopy in routine outpatient gastroenterology practice: does it work better through the nose? *Endoscopy*. 2003;35:647–651.
14. Toyoizumi H, Kaise M, Arakawa H, et al. Ultrathin endoscopy versus high-resolution endoscopy for diagnosing superficial gastric neoplasia. *Gastrointest Endosc*. 2009;70:240–245.