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# Fujinon intelligent color enhancement for the diagnosis of early esophageal squamous cell carcinoma and precancerous lesion

**ESOPHAGUS**

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Original Article

## ABSTRACT

**Background/Aims:** Esophageal squamous cell carcinoma is a common malignant tumor in recent years, and the key for improving the survival rate is early diagnosis and treatment. Computed virtual chromoendoscopy with the Fujinon intelligent color enhancement (FICE) system was reported to improve visualization of neoplastic and non-neoplastic lesions in gastroscopy and colonoscopy. The purpose of this study was to evaluate the value of FICE in the diagnosis of early esophageal squamous cell carcinoma and precancerous lesions.

**Materials and Methods:** Two hundred fifty-seven patients with suspicious lesions of the esophagus were examined successively by FICE, magnifying FICE, Lugol chromoendoscopy, and magnifying Lugol chromoendoscopy in the hospital. The lesions and the intrapapillary capillary loop (IPCL, microvessels at the surface of esophageal carcinoma) were observed and compared with the pathologic diagnosis that was regarded as the golden standard.

**Results:** The positive rates of early esophageal squamous cell carcinoma were 92.6% and 88.9% as examined by FICE and Lugol chromoendoscopy ($p>0.05$), and 96.3% and 92.6% as examined by magnifying FICE and magnifying Lugol chromoendoscopy ($p>0.05$), respectively. The magnifying FICE could observe the IPCL of the esophagus clearly. Early esophageal squamous cell carcinoma and high-grade intraepithelial neoplasia were mainly type IV and type V. Low-grade intraepithelial neoplasia and esophagitis were type II and type III, and normal esophagus was type I; however, the observation of the IPCL by magnifying Lugol chromoendoscopy was not clear.

**Conclusion:** Fujinon intelligent color enhancement and magnifying FICE are complements to Lugol chromoendoscopy and magnifying Lugol chromoendoscopy in the diagnosis of early esophageal lesions.

**Keywords:** Fujinon intelligent color enhancement, intrapapillary capillary loop, early esophageal squamous cell carcinoma

## INTRODUCTION

Esophageal carcinoma is the eighth most common carcinoma in the world, and the mortality is the sixth highest (1,2). In China, the morbidity and mortality are higher than anywhere in the world and more than 90% of esophageal carcinomas are squamous cell carcinomas (3). As the symptoms are usually inconspicuous, most patients have been at advanced stages when they come to the hospital. Many researchers have proven that 5-year survival rate of early esophageal squamous cell carcinoma patients who are treated by endoscopies may be more than 84% (4-6). So, it is important for the patients to be diagnosed at the early stage. With the rapid renewal of endoscopies, the detection rate and the diagnostic accuracy of early esophageal lesions were greatly improved. The Fujinon intelligent color enhancement (FICE) is a new diagnostic method to determine tumor margins and depth by observing the intrapapillary capillary loop (IPCL, microvessels at the surface of esophageal carcinoma) through using a magnifying mode (7). In this study, we compared FICE with Lugol chromoendoscopy and magnifying FICE with magnifying Lugol chromoendoscopy in the diagnosis of early esophageal squamous cell carcinoma and precancerous lesions in order to investigate the diagnostic value of FICE.

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## MATERIALS AND METHODS

### Patients and conceptual knowledge

All the patients had been informed before endoscopy examination and they agreed to participate in the examination. Ethical approval was agreed by the Medical Ethics Committee of Renmin Hospital of Wuhan University. Between January 2010 and January 2011, the patients who were diagnosed by conventional endoscopies in our hospital with suspicious lesions of the esophagus were selected for the study. Esophageal squamous epithelium with severe dysplasia and carcinoma in situ was defined as precancerous lesions. Mucosal cancer and submucosal cancer without lymph node metastasis of early esophageal cancer were defined as early esophageal squamous cell carcinomas (8). According to the World Health Organization and Vienna classification, we classified severe dysplasia and carcinoma in situ as high-grade intraepithelial neoplasia and classified mild to moderate dysplasia as low-grade intraepithelial neoplasia (9,10).

### Endoscopy equipment and reagent

In this study, we used a magnifying endoscope (EG-590ZW, Fujinon, Inc, Saitama, Japan), which was in combination with a light source (XL-4400. Fujinon, Inc, Saitama, Japan) and an image processor (VP-4400, Fujinon, Inc, Saitama, Japan). Of the 10 factory default modes in this endoscopy, we selected the three most appropriate ones in this study. Besides the endoscope, we also needed a reagent, 2% Lugol iodine solution.

### Procedure

This study was conducted by a senior doctor who was familiar with endoscopic operations and had rich experience using the FICE system in endoscopic procedures for more than 2 years. Firstly, we checked esophageal mucosa by conventional endoscopy under a white light and then converted it to the FICE mode in the same endoscopic procedure by a simple push of a button for further observation. When lesions were found, we would observe them more clearly in FICE modes A, B, and C, respectively. Until the lesions were shown most clearly, we recorded and saved the best wavelength combinations. Secondly, we changed the mode to magnifying FICE, which could observe the IPCL of the esophageal mucosa. All images of each lesion were taken in single view to evaluate the same IPCL as far as possible. Thirdly, after the FICE and magnifying FICE, we would stain the lesions by 2% Lugol iodine solution, which was sensitive for early esophageal squamous cell carcinoma (11). Then, the lesions were observed by Lugol chromoendoscopy and magnifying Lugol chromoendoscopy. Lastly, the lesions were resected by biopsy and diagnosed by pathological examination, which was the gold standard for esophageal squamous cell carcinoma.

### Diagnostic criteria

For detecting early-stage esophageal squamous cell carcinoma by Lugol chromoendoscopy, the unstained areas, which might be the abnormal esophagus, were discriminated (12). But, the lesions that were stained by different wavelength combinations of FICE were positive results, and the unstained ones were negative results. On this condition, the positive results might be abnormal esophagus. Then, the suspicious abnormal esophagus would be diagnosed by pathologic diagnosis. The various IPCL changes were classified as follows: dilatation, tortuosity, caliber change, and variety of shapes (13). The IPCL types in this study were based on our personal observation in our unit and from the published literature (13-15).

Type I (normal epithelial): normal IPCL with regular shape and size

Type II (like esophagitis): slight dilatation or elongation

Type III (mild dysplasia): slightly irregular or abnormal branch

Type IV (severe dysplasia): no more than three of the four kinds of changes as mentioned above

Type V (carcinoma): all of the four changes as mentioned above

### Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc, Chicago, IL, USA). The chi-square test was used to compare the lesion detections between different endoscopy images and pathologic diagnoses. A p value of less than 0.05 was accepted as statistically significant.

## RESULTS

### General results

A total of 257 patients with suspicious lesions of the esophagus had been selected for this study, including 155 males and 102 females, aged from 32 to 84 years, with a mean of 58 years. Pathologic diagnoses were as follows: 27 early esophageal squamous cell carcinomas (10.4%), 22 high-grade intraepithelial neoplasia (8.6%), 40 low-grade intraepithelial neoplasia (15.6%), 156 esophagitis (60.7%), and 12 normal esophagus (4.7%).

### Positive rates and pathological results

The positive rate of FICE in the diagnosis of early esophageal squamous cell carcinoma was 92.6% (25/27), and the positive rate of Lugol chromoendoscopy was 88.9% (24/27). There was no significant difference between these two methods (P=0.642). The positive rate of magnifying FICE was 96.3% (26/27), and the positive rate of magnifying Lugol chromoendoscopy was 92.6% (25/27). There was no significant difference between these two methods, either (p=0.556) (Table 1).

### Magnifying endoscopy images and pathological results

The pit patterns of early esophageal squamous cell carcinoma and high-grade intraepithelial neoplasia as examined by mag-

**Table 1.** The relationship of endoscopic diagnoses and pathological results

| | | Pathological Diagnoses | | | | |
|---|---|---|---|---|---|---|
| **Endoscopy** | **Total number (n)** | **Early esophageal squamous cell carcinoma (n)** | **High-grade intraepithelial neoplasia (n)** | **Low-grade intraepithelial neoplasia (n)** | **Esophagitis (n)** | **Normal esophagi (n)** |
| LC | | | | | | |
| Negative (-) | 38 | 3 | 5 | 9 | 13 | 8 |
| Positive (+) | 219 | 24 | 17 | 31 | 143 | 4 |
| FICE | | | | | | |
| Negative (-) | 29 | 2 | 3 | 5 | 9 | 10 |
| Positive (+) | 228 | 25 | 19 | 35 | 147 | 2 |
| M LC | | | | | | |
| Negative (-) | 22 | 2 | 2 | 2 | 5 | 11 |
| Positive (+) | 235 | 25 | 20 | 38 | 151 | 1 |
| M FICE | | | | | | |
| Type IV+V | 47 | 26 | 21 | 0 | 0 | 0 |
| Type II+III | 195 | 1 | 1 | 39 | 154 | 0 |
| Type I | 15 | 0 | 0 | 1 | 2 | 12 |

LC: lugol chromoendoscopy; FICE: fujinon intelligent color enhancement; MLC: magnifying lugol chromoendoscopy; MFICE: magnifying fujinon intelligent color enhancement; n: number of each group

nifying FICE were mainly type IV and type V, and the percentages were 96.3% (26/27) and 95.5% (21/22), respectively. However, the pit patterns of low-grade intraepithelial neoplasia and esophagitis were mainly type II and type III (97.5%, 98.7%), and normal esophagus was type I (100%). On the contrary, the pit patterns could not be seen clearly by magnifying Lugol chromoendoscopy.

### Side effects

There were no side effects by FICE and magnifying FICE; however, the total side effect rate of Lugol chromoendoscopy and magnifying Lugol chromoendoscopy was 12.8% (33/257). Among the 33 patients, there were 24 cases with retrosternal discomfort, 6 cases with bucking, and 3 cases with vomiting. The reasons why patients got side effects may be the irritation and toxicity of the esophagus caused by the oxide components of iodine as well as the sensitivity of patients and the symptoms of the disease itself (16,17). However, the side effects of the 33 patients all deviated within 12 hours without special treatment.

## DISCUSSION

Esophageal carcinoma, mainly divided into esophageal adenocarcinoma and esophageal squamous cell carcinoma, is one of the common malignant tumors in the world. For Europe and the United States, esophageal adenocarcinoma accounts for 50% or more of esophageal carcinoma (18); however, the prevalence of esophageal squamous cell carcinoma is higher in Asia, such as China and Japan, which accounts for 90% of esophageal carcinoma (19-21). The prognosis of esophageal squamous cell carcinoma, if detected at an advanced stage, is poor and worse than that of esophageal adenocarcinoma (22,23). But, the 5-year survival rate of early esophageal squamous cell carcinoma that is at an early stage is more than 90% after early aggressive treatment, while the rates of advanced esophageal carcinomas are significantly reduced; so, the key for improving the prognosis is early diagnosis and treatment (24). Precise endoscopic assessment of esophageal mucosal features is important to detect neoplastic lesions at an early stage. Currently, the diagnosis of early esophageal carcinoma can only rely on endoscopy and endoscopic biopsy, but the diagnosis rate by conventional endoscopy is very low. Although the invention of Lugol chromoendoscopy can help to diagnose early esophageal squamous cell carcinoma and precancerous lesion, the side effects are too serious, including vomiting, cough, bucking, retrosternal pain, and so on (25,26). Moreover, after spraying 2% Lugol iodine solution, peristalsis of the esophagus will be strengthened, and Lugol chromoendoscopy requires taking 1 or 2 minutes to color the whole mucosa (27). The procedure is inconvenient for endoscopists to observe the lesions. Sometimes, uneven dyeing will lead to misdiagnosis or leak diagnosis.

With the development of endoscopic techniques and equipment, the FICE system is a new dyeless imaging technique that enhances mucosal visibility, which can improve visualization of neoplastic and non-neoplastic lesions by gastroscopy and colonoscopy (28). This computed virtual chromoendoscopy technique, based on narrowing the bandwidth of the conventional endoscopic image arithmetically, can estimate the spectrum reflectance from a white-light endoscopic image and re-

constitute a color image from the wavelength. Moreover, the single-wavelength images are freely selected and assigned to red (R), green (G), and blue (B), respectively, to build and display a FICE-enhanced color image. Based on the various lesions, different spectral images will be selected (29), which can achieve the purpose of electronic virtual chromoendoscopy. Some researchers have used FICE to diagnose gastrointestinal lesions and received satisfactory results in the world (30-32). In this study, the best wavelength combinations that we selected were as follows: R=540 nm, G=490 nm, B=420 nm and R=550 nm, G=500 nm, B=470 nm, which could clearly show the lesions.

In addition, the IPCL is commonly observed in squamous cell carcinoma derived from the squamous epithelium with little or no glandular structure (33,34). So, magnifying endoscopes can be used to observe the IPCL of esophageal squamous cell carcinoma but not esophageal adenocarcinoma. As a result, we also compared magnifying FICE with magnifying Lugol chromoendoscopy in the observation of the IPCL in this study.

According to these results, the positive rate of Lugol chromoendoscopy was 88.9% in the diagnosis of early esophageal squamous cell carcinoma, which was lower than that of FICE, while the statistics showed that there was no significant difference between these two methods (p=0.642). At the same time, the positive rate of magnifying FICE was 96.3%, which was a little higher than that of magnifying Lugol chromoendoscopy, and there was no significant difference between these two methods, either (p=0.556). Moreover, the study also showed that the characteristic changes of the IPCL from the submucosal vein could be clearly observed by magnifying FICE, while magnifying Lugol chromoendoscopy failed in observing the IPCL. According to the results of the characteristic changes of the IPCL and pathologic diagnosis, we concluded that the IPCL of esophageal carcinomas and high-grade intraepithelial neoplasia might be mainly type IV and type V, and low-grade intraepithelial neoplasia and esophagitis were mainly type II and type III, but all patterns of normal esophagus were type I.

In summary, FICE and magnifying FICE could determine the pathological types and enhance the diagnosis of early esophageal squamous cell carcinoma accurately through observing the IPCL. Furthermore, the use of FICEavoids side effects observed by Lugol's solution and shortens the time of the endoscopic procedure. In other words, FICE and magnifying FICE are excellent complementary methods to Lugol chromoendoscopy and magnifying Lugol chromoendoscopy in diagnosing early esophageal squamous cell carcinoma and precancerous lesions.

**Ethics Committee Approval:** Ethics committee approval was received for this study from Medical Ethics Committee of Renmin Hospital of Wuhan University.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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## REFERENCES

1. Ajani J, D'Amico TA, Hayman JA, et al. Esophageal cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2003; 1: 14-27.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-917. **[CrossRef]**
3. Wang K, Yang CQ, Duan LP, et al. Changing pattern of adenocarcinoma of the esophagogastric junction in recent 10 years: experience at a large tertiary medical center in China. Tumori 2012; 98: 568-74.
4. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's esophagus. Gut 2008; 57: 1200-06. **[CrossRef]**
5. Shimizu M, Zaninotto G, Nagata K, Graham DY, Lauwers GY. Esophageal squamous cell carcinoma with special reference to its early stage. Best Pract Res Clin Gastroenterol 2013; 27: 171-86. **[CrossRef]**
6. Yamashina T, Ishihara R, Nagai K, et al. Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell carcinoma. Am J Gastroenterol 2013; 108: 544-51. **[CrossRef]**
7. Pohl J, May A, Rabenstein T, Pech O, Ell C. Computed virtual chromoendoscopy, a new tool for enhancing tissue surface structures. Endoscopy 2007; 39: 80-3. **[CrossRef]**
8. Zhao L, Wei W-Q, Zhao D-L, et al. Population-based study of DNA image cytometry as screening method for esophageal cancer. World J Gastroenterol 2012; 18: 375-82. **[CrossRef]**
9. Fléjou JF. [WHO Classification of digestive tumors: the fourth edition]. Ann Pathol 2011; 31 (Suppl): S27-31. **[CrossRef]**
10. Schlemper RJ, Riddell RH, Kato Y, et al. The vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47: 251-55. **[CrossRef]**
11. Dawsey SM, Fleischer DE, Wang GQ, et al. Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. Cancer 1998; 83: 220-31. **[CrossRef]**
12. Endo M, Kawano T. Detection and classification of early squamous cell esophageal cancer. Dis Esophagus 1997; 10: 155-8.
13. Goda K, Tajiri H, Ikegami M, et al. Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma. Dis Esophagus 2009; 22: 453-60. **[CrossRef]**
14. Kumagai Y, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. Endoscopy 2002; 34: 369-75. **[CrossRef]**

15. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 2004; 59: 28-95. **[CrossRef]**
16. Meyer V, Burtin P, Bour B, et al. Endoscopic detection of early esophageal cancer in a high-risk population: does Lugol staining improve video endoscopy? Gastrointest Endosc 1997; 45: 480-4. **[CrossRef]**
17. Kondo H, Fududa 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. **[CrossRef]**
18. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83: 2049-53. **[CrossRef]**
19. Yang M, Liu R, Sheng J, et al. Differential expression profiles of microRNAs as potential biomarkers for the early diagnosis of esophageal squamous cell carcinoma. Oncol Rep 2013; 29: 169-76.
20. Zhang C, Wang C, Chen X, et al. Expression profile of microRNAs in serum: a fingerprint for esophageal squamous cell carcinoma. Clin Chem 2010; 56: 1871-9. **[CrossRef]**
21. Takubo K, Aida J, Sawabe M, et al. Early squamous cell carcinoma of the oesophagus: The Japanese viewpoint. Histopathology 2007; 51: 733-42. **[CrossRef]**
22. Enzinger PC, Mayer R J. Esophageal cancer. N Engl J Med 2003; 349: 2241-52. **[CrossRef]**
23. Siewert J R, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? Semin Radiat Oncol 2006; 17: 38-44. **[CrossRef]**
24. Song PI, Liang H, Fan JH, Wei WQ, Wang GQ, Qiao YL. Long-term survival after esophagectomy for early esophageal squamous cell carcinoma in Linxian, China. J Surg Oncol 2011; 104: 176-80. **[CrossRef]**
25. Ponchon T. Endoscopic diagnosis of superficial neoplastic lesions of the digestive tract. Gastroenterol Clin Biol 2000; 24: B109-22.
26. Sreedharan A, Rembacken BJ, Rotimi O. Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy. Gut 2005; 54: 886-7. **[CrossRef]**
27. Asada-Hirayama I, Kodashima S, Fujishiro M, et al. Narrow band imaging with magnification can pick up esophageal squamous cell carcinoma more efficiently than lugol chromoendoscopy in patients after chemo radio therapy. Diagn Ther Endosc 2013; 2013: 256439. **[CrossRef]**
28. Buchner AM, Wallace MB. Future expectations in digestive endoscopy: competition with other novel imaging techniques. Best Pract Res Clin Gastroenterol 2008; 22: 971-87. **[CrossRef]**
29. Ringold DA, Sikka S, Banerjee B. High-contrast imaging (FICE) improves visualization of gastrointestinal vascular ectasias. Endoscopy 2008; 40 (Suppl 2): E26. **[CrossRef]**
30. Osawa H, Yoshizawa M, Yamamoto H, et al. Optimal band imaging system can facilitate detection of changes in depressed-type early gastric cancer. Gastrointest Endosc 2008; 67: 226-34. **[CrossRef]**
31. Togashi K, Osawa H, Koinuma K, et al. A comparison of conventional endoscopy, chromoendoscopy and optimal band imaging system for the differentiation of neoplastic versus nonneoplastic colon polyps. Gastrointest Endosc 2009; 69: 734-41. **[CrossRef]**
32. 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. **[CrossRef]**
33. Inoue H, Sasajima K, Kaga M, et al. Endoscopic in vivo evaluation of tissue atypia in the esophagus using a newly designed integrated endocytoscope: a pilot trial. Endoscopy 2006; 38: 891-5. **[CrossRef]**
34. Inoue H. [Endoscopic diagnosis of tissue atypism (EA) in the pharyngeal and esophageal squamous epithelium; IPCL pattern classification and ECA classification]. Kyobu Geka 2007; 60: 768-75.