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ORIGINAL ARTICLE

Observational Study

Gastric and duodenal polyps in familial adenomatous polyposis patients: Conventional endoscopy *vs* virtual chromoendoscopy (fujinon intelligent color enhancement) in dysplasia evaluation

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Abstract

AIM

To test the fujinon intelligent color enhancement (FICE) in identifying dysplastic or adenomatous polyps in familial adenomatous polyposis (FAP) patients.

METHODS
Seventy-six consecutive FAP patients, already treated by colectomy and members of sixty-five families, were enrolled. A FICE system for the upper gastro-intestinal tract with an electronic endoscope system and a standard duodenoscope (for side-viewing examination) were used by two expert examiners. Endoscopic resection was performed with diathermic loop for polyps ≥ 6 mm and with forceps for polyps < 6 mm. Formalin-fixed biopsy specimens were analyzed by two expert gastrointestinal pathologists blinded to size, location and number of FAP-associated fundic gland polyps.

RESULTS
Sixty-nine (90.8%) patients had gastric polyps (34 only in the corpus-fundus, 7 only in the antrum and 28 in the whole stomach) and 52 (68.4%) in duodenum (7 in the bulb, 35 in second/third duodenal portion, 10 both in the bulb and the second portion of duodenum). In the stomach fundus after FICE evaluation, 10 more polyps were removed from 10 patients for suspicious features of dysplasia or adenomas, but they were classified as cystic fundic gland after histology. In the antrum FICE identified more polyps than traditional endoscopy, showing a better tendency to identify adenomas and displastic areas. In the duodenum FICE added a significant advantage in identifying adenomas in the bulb and identified more polyps in the Ⅱ/Ⅲ portion.

CONCLUSION
FICE significantly increases adenoma detection rate in FAP patients but does not change any Spigelman stage and thus does not modify patient's prognosis and treatment strategies.

Key words: Fujinon intelligent color enhancement; Familial adenomatous polyposis; Spigelman; Endoscopy; Polyp; Adenoma; Stomach; Duodenum

Core tip: Colon endoscopic surveillance and prophylactic colectomy have strongly reduced mortality due to colorectal carcinoma and have improved survival of familial adenomatous polyposis (FAP) patients, leading to the development of surveillance for extra-colonic cancers. Polyps in the duodenum and stomach are frequent findings in FAP. The timing of endoscopic and histology surveillance is currently a great challenge. Spectral estimation by fujinon intelligent color enhancement (FICE) may identify dysplasia and discriminate between adenomatous and non-adenomatous polyps. Interestingly, application of FICE to FAP patients significantly increases the detection of adenomas but does not yet change the prognosis, surveillance program and treatment strategies.

Lami G, Galli A, Macrì G, Dabizzi E, Biagini MR, Tarocchi M, Messerini L, Valanzano R, Milani S, Polvani S. Gastric and duodenal polyps in familial adenomatous polyposis patients: Conventional endoscopy *vs* virtual chromoendoscopy (fujinon intelligent color enhancement) in dysplasia evaluation. *World J Clin Oncol* 2017; 8(2): 168-177 Available from: URL: http://www.wjgnet.com/2218-4333/full/v8/i2/168.htm DOI: http://dx.doi.org/10.5306/wjco.v8.i2.168

INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited syndrome characterized by the development of colorectal cancer by the age of 40 years in nearly 100% of individuals[1]. Colon Endoscopic surveillance and prophylactic colectomy have strongly reduced mortality due to colorectal carcinoma and have improved survival of FAP patients with minimal consequences[2,3], leading to the introduction of surveillance strategies for the prevention of other extra-colonic malignancies[4].

The duodenum is the second most common site of polyps development after colon, with a life-time risk of duodenal adenomas that approaches 100% in FAP affected individuals[5,6]. The cumulative risk of duodenal cancer or high grade of dysplasia by the age of 60 years is 4%-10%[6-8].

Endoscopic surveillance and removal of neoplastic tissue is useful in the prevention of duodenal cancer[8]. However, the choice of treatment and the optimal timing of surveillance based on endoscopic and histopathology examination for each patient is currently a great challenge. Currently the surveillance of duodenum is based on the Spigelman classification of duodenal adenomatosis (Table 1); however, this staging system has low predictive values and has never been validated[6,8].

Gastric polyps are also a common finding in patients with FAP: they mostly consist of FAP-associated fundic gland polyps (FGPs) reported to occur at variable rates, up to 88%[9,10], against a strongly smaller rate (0.8%-5.0%)[11,12] in non-FAP subjects who undergo an esophagogastroduodenoscopy (EGD).

FGPs have historically been considered non-neoplastic lesions without malignant potential[13]; however recent studies have questioned this assumption reporting high rates of low and high grade dysplasia (up to 54%)[9,14,15]. In particular, European and Asian registries of FAP patients proved the presence of gastric carcinoma arising from FGPs in FAP patients and an incidence of gastric adenocarcinoma between 0.6% and 4.0%[16-19].

Other common types of gastric polyps are represented by adenomas (gastric foveolar or intestinal type-gastric adenomas and pyloric gland adenomas) which are reported in approximately 10% of gastric polyps in FAP patients[10,20,21] and which can arise in the gastric antrum, in the gastric body-fundus or in the context of FGP[22]. So, identification of dysplastic lesions or adenomatous tissue in these patients is often made difficult by the great number of polyps (up to hundreds) and by the patchy

Table 1 Demographic features

Features	Patients
Total	76
Age (yr)	Mean 40.3 (24-64)
Gender	
Male	41 (53.9%)
Female	35 (46.1%)
Prior surgery	
IRA	10 (13.2%)
IPAA	66 (86.8%)
Chemoprevention	16 (21.1%)
NSAIDS intake	17 (22.4%)
Tobacco exposure	21 (27.6%)
PPI/anti-H2 intake	14 (18.4%)
Family history of GI malignancies	
None	31 (40.8%)
1 member	32 (42.1%)
2 members	10 (13.2%)
3 members	3 (3.9%)
Spigelman duodenal stage	
0	28 (36.8%)
I	7 (9.2%)
II	34 (44.8%)
III	7 (9.2%)
IV	0 (0.0%)

IRA: Total colectomy and ileo-rectal anastomosis; IPAA: Total proctocolectomy and ileopouch-anal anastomosis; NSAIDS: Non steroidal anti-inflammatory drugs; PPI: Proton pump inhibitors.

distribution of dysplasia.

By now, dysplasia finding in this subgroup of subjects is made on the basis of random biopsies[9] which lead to a time consuming, laborious and poorly performing procedure, that can result in a high rate of missed lesions. According to that, it would be useful identifying FGPs at risk of malignant degeneration.

A better characterization of patients, an optimized program of surveillance and a good survival are possible with a selective and complete asportation and with a careful histological evaluation.

It is well known that is possible to predict the histology of a mucosal lesion by observing the crypt orifices (the so called pit pattern) of mucosal glands[23] and the capillary pattern of the mucosa[24]. Several endoscopic imaging techniques have been proposed to enhance the details of these patterns[25]. Among these, chromoendoscopy is a widely applied staining method that uses biocompatible dye agents which accumulate within crypt orifices during endoscopy[26]. Although chromoendoscopy is effective for many applications, it still has some problems, such as difficulty in achieving complete and even coating of the mucosal surface with the dye, the extra cost of the equipment needed for dye spraying and the extra time required to perform the procedure. Moreover, traditional chromoendoscopy isn't able to enhance the capillary pattern, whose evaluation is essential in early diagnoses of malignant lesions[24]. In attempt to resolve these problems, other endoscopic technologies have been developed. Fujinon intelligent color enhancement (FICE™, Fujinon Corp, Saitama, Japan) represents a spectral estimation technique based on arithmetically processing of a white-light image captured by a video endoscope and sent to the spectral-estimation matrix-processing circuit. The image of the white-light endoscopic observation is resolved in each color image of the red, green and blue signal. Next, each resolved image is converted into various presumed wavelength images by a pixel unit. The images of an arbitrary single wavelength are then extracted and reconstructed. Due to its variable setting functions (up to 10) it is possible to select flexibly the most suitable wavelengths required for examination. Preliminary studies suggested that FICE successfully achieved enhancements of real-time observations of mucosal and microvascular patterns[27,28].

The light penetration into the mucosa varies according to the wavelengths: Those in the 400-500 nm range are ideal for analyzing surface structures whereas, because of the absorption properties of hemoglobin, longer wavelengths of about 550 nm are more effective for the visualization of blood vessels.

FICE seems able to discriminate between adenomatous and non-adenomatous polyps and to identify the presence of dysplasia[29-32]. Few studies have been conducted to determine the efficacy of chromoendoscopy, both traditional and virtual, in the evaluation of duodenal and peri-ampullary adenomatous polyps in FAP patients[33-35]. Interestingly, FICE application in the discrimination between neoplastic and non-neoplastic gastric lesions has not been throughly investigated[36-39], and no data are available about FICE in evaluating FGPs dysplasia or application of FICE for the screening of FAP patients.

In FAP cohort, the specific identification of who is at a greater risk of cancer development could be of paramount importance to assure a personalized program of surveillance or a therapeutic intervention.

The primary aim of this study was to assess the capability of FICE in identifying gastric polyps with dysplastic or adenomatous tissue in comparison to traditional endoscopy and in identifying a greater number of duodenal adenomas with advanced histological features.

Secondary aim was to assess the capability of FICE in identifying adenomas not seen on white light evaluation.

MATERIALS AND METHODS

Patients

Seventy-six consecutive FAP patients, already treated by colectomy and members of sixty-five families, were enrolled. Exclusion criteria were: Uncorrectable coagulopathy, inability to give informed consent, age < 18 years, prior gastro-duodenal surgery or a personal history of gastro-duodenal cancer. All patients underwent a surveillance esophagogastroduodenoscopy (EGD) in deep sedation at the Gastroenterology U.O. of the Azienda Ospedaliero Universitaria di Careggi, Firenze, Italy. Written informed consent were obtained before EGD and sedation.

Endoscopy

A FICE system (EG-590ZW; Fujinon Corp, Saitama,

Japan) for the upper gastro-intestinal tract with an electronic endoscope system (EPX-4400; Fujinon Corp, Saitama, Japan) was used for this study. In this system, ten channels with different predefined combinations of absorption wavelengths are available. We used channel 5, corresponding to R 500 nm, G 480 nm, B 420 nm, on the basis of previous studies.

A standard duodenoscope was used for side-viewing examination. Because this model of duodenoscope does not support FICE system, ampullary and periampullary evaluations were not included in the analysis. All of the endoscopic procedures were performed by two experts examiners.

"A" operator performed the exam on white light, while "B" operator used only FICE system for gastroduodenal visualization. Each EGD was divided into three phases.

During the first phase, "A" operator observed stomach and duodenum by white light recording photographic images of suspected polyps and pointing them. We intended suspected polyps on white light those larger than 1 cm and those with irregular shape or surface features.

During the second phase, "B" operator performed the exam using FICE and, like "A" operator, recorded photographic images of suspected polyps on the basis of Kudo classification[23] and capillary pattern, and pointed them.

Kudo classification classifies mucosal crypt patterns into five types, with type Ⅰ and Ⅱ predicting non-adenomatous lesions and type Ⅲ-Ⅴ predicting adenomatous lesions.

Hyperplastic polyps were suspected when the surface showed pale color with only minute thin superficial (couperose-like) vessels and round or asteroid pattern (type Ⅰ and Ⅱ). Adenomas were suspected in the presence of increased vascular density (darkening of the mucosal pattern or a fine meshwork of brownish/bluish vessels) and a typical tubular or gyrus-like pattern (type Ⅲ-Ⅳ). Finally, type V have a non structural pattern which identifies high dysplastic or yet carcinomatous lesions.

During this phase we intended suspected those lesions with a pit pattern type Ⅲ-Ⅴ and those with an increased capillary density.

During the third phase, after the two endoscopists' cross-evaluation, lesions which seemed suspected only by FICE, only by white light or by both methods were resected or biopsied according to Kudo class.

Endoscopic resection was performed with diatermic loop for polyps ≥ 6 mm and with forceps for polyps < 6 mm. The size was estimated using on open biopsy forceps (8 mm) for comparison and recorded as smaller than 6 mm, 6 to 10 mm, 11 to 20 mm and greater than 20 mm.

The total number of FGPs was documented as below: 0 to 2 polyps, 3 to 20, 21 to 30 and more than 30 polyps. On the basis of location we identified: Fundus-corpus, antrum, duodenal bulb, Ⅱ°/Ⅲ° duodenal portion.

For fundic polyps seen on white light, the number of FGPs from which a biopsy specimen was taken was based on the total number of FGPs present: 3 biopsies if 3-20 polyps, 5 biopsies if 21-30 polyps, 7 biopsies if > 30 polyps[9].

On FICE, only suspected polyps (Kudo Ⅲ-Ⅴ, high capillary density) were removed.

For antral and bulbar polyps, all of them were removed or biopsied both on withe light than on FICE.

In the second and third duodenal portion, on white light only suspected polyps were resected or biopsied, while on FICE were biopsied those with Kudo Ⅴ and those with Kudo Ⅳ and high capillary density.

Macroscopic classification of lesions followed the Paris classification[40] as polyp, superficially flat or depressed lesion, and lateral spreading tumor.

Histology

All biopsy specimens, fixed in 10% neutral buffered formalin, were analyzed by two expert gastrointestinal pathologists blinded to size, location and number of FGPs.

In the case of multiple lesions in the same patient, each lesion was identified and placed in different flasks. Lesions were histological classified in adenomatous, hyperplastic or inflammatory polyps, fundic gland polyps, and metaplastic areas.

Adenomatous polyps were classified according to OMS classification: Tubular if holding more than 75% of tubular glands, villus if holding more than 75% of villus glands, tubulo-villus if not prevailing none of the two patterns.

Dysplasia was classified according to Vienna criteria[41] in low grade if holding nuclear enlargement, stratification and hyperchromasia with overall preservation of nuclear polarity; high grade as above but with nuclear polarity loss and glandular crowding; indefinite for dysplasia if present mild nuclear enlargment and insufficient hypercromasia to be classified as dysplasia or if present a significant obscuring background inflammation.

The stage of duodenal polyposis was graded according to Spigelman classification modified sec. Saurin[42], which take into account duodenal polyp number, size, histological type and grade of dysplasia. It was noted before and after FICE evaluation.

Statistical analysis

The diagnostic performances (sensitivities, specificities, positive and negative predictive values) of FICE and WL were determined by comparing the endoscopic diagnoses with the histo-pathological findings. To identify associations of demographic, clinical and endoscopic features with the presence of FGP dysplasia or with adenomas, the Fisher exact test was used to study univariable associations of categoric demographic and endoscopic factors with the presence of dysplasia or adenomatous tissue. The Student t test was used for continuous factors. A *P* value "two tailed" < 0.05 was considered statistical significant. The strength of association was calculated by odds ratio (OR). The statistical methods of this study were reviewed by S. Milani, University of Florence.

Table 2 Stomach and duodenum polyps

	Patients		Patients
Fundus	34 (49.3%)	Bulb	7 (13.5%)
Antrum	7 (10.1%)	Ii°/iii° portion	35 (67.3%)
Fundus + antrum	28 (40.6%)	Bulb+ii°/iii°	10 (19.2%)
Total stomach	69 (100%)	Total duodenum	52 (100%)

Table 3 Features of fundic polyps identified by white light endoscopy

	P1-P3	P4-P10	P11-P24	P25-P55	P56-P397
Kudo	I	II	II	II	I
Size (mm)	5	5	6-10	5	5
Paris CL	Is	Is	Is	Is	Is
Histology	HYP	IN	FGP	FGP	FGP

IN: Inflammatory; FGP: Fundic gland polyp; IP: Hyperplastic.

RESULTS

Seventy-six consecutive FAP patients (41 male and 35 female; mean age 40.3 years old, range 24-64) underwent EGD. Among all patients, 69 (90.8%) had gastric polyps (34 only in the corpus-fundus, 7 only in the antrum and 28 in the whole stomach) and 52 (68.4%) in duodenum (7 in the bulb, 35 in second/third duodenal portion, 10 both in the bulb and the second portion of duodenum) (Table 2).

Identification of polyps in the stomach

Fundus: 62 patients had a widespread fundic polyposis (81.6%); 52 of them had more than 30 fundic polyps (68.5%), 3 between 21 and 30 (3.9%) and 7 between 5 and 20 (9.2%).

On white light visualization, 397 polyps in 62 patients (6.4 polyps per patient) were removed. Three were hyperplastic polyps, 7 inflammatory while the rest were cystic fundic gland polyps. No polyp harboured dysplasia nor adenomatous foci (specificity 100%, sensitivity NV, positive predictive value NV, negative predictive value 100%, 95%CI) (Table 3).

After FICE evaluation, 10 polyps were removed from 10 patients on the basis of suspicious features of dysplasia or adenomatous tissue. All of them were cystic fundic gland polyps, none of them harboring dysplasia or adenomatous foci (specificity 97%; sensitivity NV; positive predictive value 0%; negative predictive value 100%) (Table 4).

Thirty-eight patients with fundic polyposis had also duodenal polyposis (61.2%), while among the 14 patients without fundic polyps, 10 had polyps in the duodenum (71.4%). Thus the presence of fundic polyps doesn't correlate with a higher risk to develop duodenal polyps (P = 0.55; OR = 0.6).

Antrum: A total of 56 polyps were identified and removed in the antrum of 35 patients (average 1.6 polyps per patient). Twenty-four polyps were identified in 35 patients by white light endoscopy (0.7 polyps per patient); 21 of them were tubular adenomas with low grade dysplasia while 3 were inflammatory polyps (specificity 88.0%; sensitivity 67.7%; positive predictive value 87.5%; negative predictive value 68.7%) (Table 5).

Beside polyps seen with conventional endoscopy, FICE was further able to identify 32 polyps in 28 patients. They were 7 tubular adenomas with low grade dysplasia, 14 inflammatory polyps, 3 areas with low grade dysplasia in the context of flogistic mucosa, 8 metaplasic areas (specificity 12.0%; sensitivity 100%; positive predictive value 58.5%; negative predictive value 100%) (Table 6).

FICE identified a higher number of polyps than traditional endoscopy (56 *vs* 24; $P < 0.0001$), showing a better, but not statistically significant, tendency to identify adenomas and displastic areas (31 *vs* 21; $P = 0.0857$). All but 4 polyps missed out by white light, were flat.

Eighteen of patients with antral lesions (51.4%) had polyps also in the duodenum. There is no relationship between presence of dysplasia in antral stomach and Spigelman advanced stages (P = 1; OR = NV).

Table 4 Features of fundic polyps identified by fujinon intelligent color enhancement

	P1-P6	P7-P10
Kudo	IIIS	IIIL
Size (mm)	5	5
Paris CL	Is	Is
Histology	FGP	FGP

FGP: Fundic gland polyp.

Table 5 Features of antral polyps identified by white light endoscopy

	P1-P3	P4	P5-P10	P11-P17	P18-P24
Kudo	II	IIIS	IIIS	IIIS	IV
Size (mm)	6-10	6-10	5	5	5
Paris CL	IIa	IIa + IIc	Is	Is	Is
Histology	IN	TA, LGD	TA, LGD	TA, LGD	TA, LGD
Spigelman	0	0	I°	0	0

IN: Inflammatory; TA: Tubular adenoma; LGD: Low grade dysplasia.

Identification of duodenal polyps

Bulb: 21 polyps were seen in 17 patients (1.2 polyps per patient). All of them were endoscopically removed. White light endoscopy identified 14 polyps in 12 patients; 8 polyps were inflammatory, while 6 were tubular adenomas with low grade dysplasia (specificity 0%; sensitivity 46.2%; positive predictive value 42.9%; negative predictive value 0%) (Table 7).

During FICE evaluation, beside polyps seen with conventional endoscopy, 7 more polyps in 7 patients, five

Table 6 Features of antral polyps identified by fujinon intelligent color enhancement

	P25	P26	P27	P28-P30	P31	P32-P33	P34-P35	P36-P38	P39-P44	P45-P49	P50-P53	P54-P56
Kudo	V	V	IIIS	IIIL	IIIL	IV	IV	IIIL	IIIL	IIIS	IIIS	V
Size (mm)	5	5	5	6-10	5	5	6-10	5	5	5	6-10	5
Paris CL	IIb	IIa	IIb	IIb	IIa	IIb	IIa	IIa	IIb	IIb	Is	IIb
Histology	IN LGD	IN LGD	IN LGD	MET	MET	MET	MET	IN	IN	IN	TA LGD	TA LGD
Spigelman	III°	II°	I°	II°	II°	0	II°	0	0	0	I°	II°

IN: Inflammatory; TA: Tubular adenoma; LGD: Low grade dysplasia; MET: Metaplasia.

Table 7 Features of bulbal polyps identified by white light endoscopy

	P1-P5	P6-P8	P9	P10-P12	P13	P14
Kudo	II	IIIS	IIIS	IIIL	IV	IV
Size (mm)	5	6-10	6-10	5	6-10	6-10
Paris CL	Is	Is	Is	IIa	Is	Is
Histology	IN	TA LGD	TA LGD	IN	TA LGD	TA LGD
Spigelman	0	II°	I°	0	III°	II°

TA: Tubular adenoma; LGD: Low grade dysplasia.

Table 8 Features of bulbal polyps identified by fujinon intelligent color enhancement

	P15	P16-P17	P18	P19	P20-P21
Kudo	IIIS	IV	IIIS	IIIL	IIIS
Size (mm)	5	6-10	6-10	5	5
Paris CL	IIa	IIb	IIa	IIb	IIb
Histology	TA LGD	TA LGD	TA LGD	TA LGD	TA LGD
Spigelman	I°	II°	II°	I°	I°

TA: Tubular adenoma; LGD: Low grade dysplasia.

of them new, were discovered. All of them were tubular adenomas with low grade dysplasia (specificity 62.5%; sensitivity 100%; positive predictive value 81.3%; negative predictive value 100%) (Table 8).

FICE was able to see further 7 polyps than traditional endoscopy, and it was able to identify a quite significant higher number of polyp in the duodenal bulb (21 *vs* 14; $P = 0.069$). FICE added a statistical significant advantage in identifying adenomas (13 *vs* 6; $P = 0.03$). All FICE identified polyps were flat lesions. All patients with bulbal polyps had also lesions in the gastric fundus and no adenoma in the antrum.

All patients with bulbal adenomas had polyps in the second/third portion of duodenum, while patients with inflammatory polyps had a Spigelman's stage 0.

II°/III° duodenal portion: Totally, 391 polyps in 45 patients (8.7 polyps per patient) were identified. Of them, 105 were removed or biopsied (26.5%). Conventional endoscopy identify 324 polyps in 45 patients (7.2 polyps per patient). Of them, 94 were removed or biopsied (2.1 polyps per patient) and they resulted: 80 tubular adenomas with low grade dysplasia, 10 inflammatory polyps and 4 tubulo-villous adenomas with low grade dysplasia. No case of high grade dysplasia (3 suspected). (Table 9). FICE identified further 67 polyps in 35 patients and 11 were removed or biopsied in 11 subjects. All of them were tubular adenomas with low grade dysplasia. No case of high grade dysplasia (Table 10). FICE was able to identify a higher number of polyps than traditional endoscopy (8.7 *vs* 7.2; $P < 0.001$). All polyps not seen on white light were flat lesions.

Thirty-five of patients with duodenal polyposis had also polyps in the fundus, 4 had adenomas and 2 dysplastic areas in the antrum, thus FICE didn't change any Spigelman stage just defined with conventional endoscopy.

DISCUSSION

Duodenal adenomatous polyps are common manifestations of FAP found in 30% to 90% of patients, with a life time risk approaching 100%[5,6,43]. While rare in the general population (0.01%-0.04% of incidence at an average age of 65 years)[43], the risk of duodenal or periampullary cancer is increased several hundreds fold in FAP patients (estimated cumulative risk of 4.5% by age 57 and a median age at presentation of 52 years)[6,8]. Duodenal cancer is the second most common cause of disease-related mortality in patients with FAP, only the

Table 9 Features of duodenal polyps identified by white light endoscopy

	Kudo	Size (mm)	Paris CL	Histology	Spigelman
P1-P4	Ⅳ	11-20	Ⅱa	TA LGD	Ⅲ°
P5-P7	Ⅴ	6-10	Ⅱa	TA LGD	Ⅱ°
P8-P11	Ⅳ	5	Ⅱb	TA LGD	Ⅱ°
P12-P16	ⅢS	6-10	Ⅱa	TVA LGD	Ⅲ°
P17-P27	ⅢS	5	Ⅱa	TA LGD	Ⅱ°
P28-P34	ⅢS	5	Ⅱa	TA LGD	Ⅰ°
P35-P40	ⅢS	5	Ⅱb	TA LGD	Ⅱ°
P41-P43	ⅢS	5	Ⅰs	TA LGD	Ⅱ°
P44-P47	ⅢS	5	Ⅰs	TA LGD	Ⅰ°
P48-P50	ⅢS	11-20	Ⅱa	TA LGD	Ⅱ°
P51-P58	ⅢL	5	Ⅱb	TA LGD	Ⅱ°
P59-P65	ⅢL	5	Ⅱa	TA LGD	Ⅱ°
P66-P68	ⅢL	6-10	Ⅱa	TA LGD	Ⅱ°
P69-P72	ⅢL	6-10	Ⅱa	TA LGD	Ⅲ°
P73-P79	ⅢL	6-10	Ⅱb	TA LGD	Ⅱ°
P80-P84	Ⅱ	5	Ⅱa	TA LGD	Ⅲ°
P85-P91	ⅢL	5	Ⅱb	IN	Ⅱ°
P92-P94	ⅢS	5	Ⅱa	IN	Ⅰ°

IN: Inflammatory; TA: Tubular adenoma; LGD: Low grade dysplasia.

Table 10 Features of duodenal polyps identified by fujinon intelligent color enhancement

	P95-P97	P98-P100	P101-P102	P103-P105
Kudo	Ⅳ	Ⅳ	Ⅴ	Ⅳ
Size (mm)	5	6-10	6-10	5
Paris CL	Ⅱa	Ⅱb	Ⅱb	Ⅱb
Histology	TA LGD	TA LGD	TA LGD	TA LGD
Spigelman	Ⅰ°	Ⅱ°	Ⅱ°	Ⅱ°

TA: Tubular adenoma; LGD: Low grade dysplasia.

second to advanced and metastatic colorectal cancer. A regular and careful program of endoscopic surveillance is worthwhile in identifying early pre-malignant lesions.

Gastric polyps, particularly fundic polyps, are considered always non-neoplastic lesions, also in FAP and non-FAP patients; nonetheless high rate of their prevalence (20%-88%)[6,9-11] and several cases of dysplasia in FGPs in FAP have been recently reported, with rate of incidence up to 54%[9-11,18].

Chromoendoscopy, both traditional and virtual, has been proven to be a good tool to increase polyps identification rate and to predict their histology[29-32]. Only one study was published on the use of FICE in the evaluation of duodenal lesions[44]. This study was conducted using a double balloon enteroscopy on patients with duodenal lesions. In this study only two FAP patients were included and FICE enhanced mucosal pattern of these polyps, and it correlated with the increase of detection of more lesions.

However, neither previous studies using traditional chromoendoscopy nor FICE, were conducted in evaluation of gastric polyps in FAP patients. To the best of our knowledge, our study is the first that has assessed the role of FICE in FGPs dysplasia identification and in the gastroduodenal polyps characterization in FAP subjects.

In agreement with the literature's data, the prevalence of gastric polyps was relatively elevated (90.8%), while duodenal polyps were diagnosed in 68.4% of patients, slightly lower than the reported literature value.

In the majority of FAP subjects (62/76; 83.3%), gastric polyps were so numerous that they carpeted the fundic mucosa, making difficult identifying dysplasia by random biopsies on the basis of the total number of polyps, as indicated in a recent study conducted by Bianchi *et al*[9]. Consequently, having an endoscopic technique able to target fundic biopsies is important to overcome this issue. Moreover, Bianchi *et al*[9] reported a prevalence of dysplasia in fundic polyps of 42%, while we have found only fundic gland polyps without displastic or adenomatous areas, although we have followed their sampling method. A possible explanation to this marked mismatch, could lie in the size of the polyps removed: we did found only subcentimetric polyps, while Bianchi *et al*[9] have demonstrated that the risk of dysplasia correlated with polyp size. No polyps removed had suspected superficial features according to Kudo classification, while Bianchi *et al*[9] did not adopted any classification to describe mucosal and vascular pattern; consequently we don't know if their removed polyps had or not a suspected pattern.

FICE pointed our attention on 10 fundic polyps, that seemed suspected for harboring adenomatous tissue;

however histological results did not confirmed this suspect and all of polyps resulted fundic gland polyps. In this case, FICE has not increased the identification rate of dysplasia or adenomatous tissue in fundic polyps.

Prevalence of patients with antral adenomas was about 21.1% (16/76), more than reported in the Western World data, but consistent with Japanese findings. The use of FICE could explain our result, since it has increased the identification rate of antral adenomas compared to white light, with a difference near to statistical significance (P = 0.0857).

The very low specificity of the method (12.0%) could be explained by the presence of phlogosis (in fact almost all false positive harbored flogistic areas) able to distort the mucosal and vascular pattern, specifically enhanced by virtual chromoendoscopy.

Therefore, FICE allows to identify a greater number of adenomas to the detriment of a greater number of biopsies. Anyway this approach didn't determine a different timing in the surveillance program, but changed the attention on the antral evaluation during the following endoscopies. In duodenal bulb FICE was able to identify more adenomas than traditional endoscopy (P = 0.03). Furthermore, all patients with FICE-identified adenomas had polyps in the duodenum too, thus the identification of bulbar adenomas didn't modify surveillance timing.

Taking into account also bulbar polyps, duodenal adenomas prevalence in FAP patients was 68.4%, with low Spigelman stages (9.2% stage Ⅲ e 0% stage Ⅳ). In duodenum, FICE has allowed to see a greater number of adenomas than white light (P < 0.001), without no modifications of Spigelman stage neither identification of high grade dysplasia.

Among FICE identified polyps, 4 lesions were suspected for high grade dysplasia, but three were inflammatory polyps at histopathological examination and one was a tubular adenoma with low grade of dysplasia. Other 7 polyps (Kudo IV) had an increased capillary density but they were tubular adenomas with low grade of dysplasia.

Finally, in duodenum, FICE increased the polyps detection rate but didn't change any Spigelman stage determined with conventional endoscopy. These data are in agreement with the little size and the absence of high grade dysplasia. Moreover this method wasn't able to modify FAP patients' prognosis, polyps' surveillance program and their therapeutic management. We did not find any relationship between the presence of gastric polyps, duodenal polyposis and high Spigelman stage (P = 1).

Adenomas were 435 and 81 of them were diagnosed only by FICE that was able to identify a significative higher number of adenomas (P = 0.0062). Overall, FICE has specificity, sensitivity,positive and negative predictive values higher than traditional endoscopy referring to adenomas (96.0% *vs* 7.1%; 98.8% *vs* 80.2%; 90.3% *vs* 44.9%; 98.8% *vs* 27.6%, respectively; P < 0.0001). Conversely, it wasn't possible to correlate for high grade dysplasia due the absence of dysplastic lesions according to the histopathological examination.

The FICE identified lesions (106/468; 22.6%) were mostly flat (67.9%; P = 0.029) and small (all below 1 cm). According to already published data, FICE was particularly able to identify polyps with these features. It isn't clear if this ability might have clinical and procedural consequences.

In summary, in our study, FICE, like traditional endoscopy, could not identify any adenoma at risk of malignant transformation probably as a consequence of patients features (*e.g.,* favorable genotype, recent EGD).

Nonetheless FICE significantly increases adenoma detection rate (P = 0.0062) but does not change any Spigelman stage and thus does not modify patient' s prognosis, surveillance program and treatment strategies. Probably a careful patient selection, an accurate histological examination, a concomitant use of lateral viewing endoscope, could make FICE gain that role who everybody expects in FAP patient.

COMMENTS

Background

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited syndrome characterized by the development of colorectal cancer by the age of 40 years in nearly 100% of individuals. The use of colon endoscopic surveillance and prophylactic colectomy have strongly reduced mortality in FAP patients leading to the introduction of surveillance strategies for the prevention of other extracolonic malignancies (*e.g.,* in the duodenum and in the stomach). Duodenal adenomatous polyps are common manifestations of FAP found in 30% to 90% of patients. Duodenal cancer is the second most common cause of disease-related mortality in patients with FAP, only the second to advanced and metastatic colorectal cancer. Gastric polyps, particularly fundic polyps, are considered always non-neoplastic lesions, also in FAP and non-FAP patients; nonetheless high rate of their prevalence (20%-88%) and several cases of dysplasia in FGPs in FAP have been recently reported, with rate of incidence up to 54%.

Research frontiers

The observation of the pit and capillary patterns of the mucosal glands and the mucosa, respectively, by chromoendoscopy might predict the histology of mucosal lesions.

Innovations and breakthroughs

Chromoendoscopy is a staining method that uses biocompatible dye agents which accumulate within crypt orifices during endoscopy. Chromoendoscopy has difficulty in achieving complete and even coating of the mucosal surface with the dye, requires the extra cost for the of the dye spraying equipments and extra time to perform the procedure. Fujinon Intelligent Color Enhancement (FICE™, Fujinon Corp, Saitama, Japan) is a spectral estimation technique based on arithmetically processing of a white-light image captured by a video endoscope and sent to the spectral-estimation matrix-processing circuit. Preliminary studies suggested that FICE successfully achieves enhancements of real-time observations of mucosal and microvascular patterns and may discriminate between adenomatous and non-adenomatous polyps and it may identify the presence of dysplasia. In the study, FICE, like traditional endoscopy, could not identify any adenoma at risk of malignant transformation probably as a consequence of patients features. However FICE significantly increases adenoma detection without changing patient's prognosis, surveillance program and treatment strategies. Probably a careful patient selection, an accurate histological examination, a concomitant use of lateral viewing endoscope, could make FICE gain that role who everybody expects in FAP patient.

Applications

The timing of endoscopic and histology surveillance is currently a great challenge. Spectral estimation by fujinon intelligent color enhancement (FICE) may identify dysplasia and discriminate between adenomatous and non-adenomatous polyps.

Terminology

FAP is an autosomal dominant inherited syndrome who invariably develops to colorectal cancer by the age of 40 years in nearly 100% of individuals. Several endoscopic imaging techniques have been proposed to enhance the detail of these patterns. Among these, chromoendoscopy is a staining method applied in endoscopy that uses biocompatible dye agents which accumulate within crypt orifices. FICE is a modern endoscopic spectral estimation technique that successfully enhances the observation of mucosal and micro-vascular patterns.

Peer-review

The presented results, obtained with 76 FAP patients, indicate that FICE assay offers considerable advantage over traditional chromoendoscopy to discriminate between adenomatous and non-adenomatous polyps. The authors, however, caution that the application of FICE to FAP patients while helpful in prediction the histology of the mucosal lesion and significantly increases the detection of adenomas, do not change the prognosis and treatment.

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