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FICE in Predicting Colorectal Flat Lesion Histology

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ABSTRACT

Background and Objectives: Colonoscopy is the gold standard for detection of polyps and is preventive against colorectal cancers. Flat adenomas are small, superficial lesions and have a high rate of going undetected during conventional white-light endoscopy. This article adds to the scant body of literature in English regarding in vivo detection and diagnosis of flat adenomas using Fujinon intelligent color enhancement (FICE) system. In this study, we investigated the diagnosis of flat lesions via the FICE endoscopy system and in vivo histologic diagnostic estimations of flat lesions.

Methods: This prospective study was conducted in patients who underwent colonoscopy that found flat adenomas. Lesions were classified morphologically with regard to the Paris Classification and sent for histopathologic examination after in vivo histologic diagnostic estimations were made according to Kudo's pit pattern classification. The positive predictive value (PPV), negative predictive value (NPV), specificity, sensitivity, and accuracy of in vivo endoscopic diagnostic estimations of flat lesions with the FICE system were analyzed.

Results: A total of 217 flat lesions were identified in 137 patients. Of the lesions, 85.7% were Paris type 0-IIa, and 59.4% were Kudo pit pattern type III. When the FICE diagnostic estimations of flat lesions and final pathology results were considered, PPV was 68.5%, NPV value was 89.6%, sensitivity was 94.7%, specificity was 50.9%, and accuracy was 74.2%.

Conclusions: Biologic importance of flat lesions is obscure, as they are usually missed during colonoscopy. The use of novel endoscopic techniques may improve their detection and diagnosis rates.

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INTRODUCTION

Colorectal cancer is one of the most common types of cancer worldwide and is the third most common cause of cancer-related death among women and the fourth among men.[1] Most colorectal cancers are sporadic and develop from adenomatous polyps according to the adenoma–carcinoma sequence hypothesis.[2] In the Western population, there is a 50% incidence of polyps among populations aged over 50.[3] Colorectal cancers, which develop from polyps, generally protrude toward the lumen and cause obstruction. Flat adenomas, on the other hand, are superficial lesions that mostly cause ulcerous tumors and tumor perforation of the colon wall. The gold standard in the diagnosis of colorectal cancers and cancer precursor polyps is colonoscopy.[4] The removal of adenomatous polyps via colonoscopy prevents the development of colorectal cancers. It is therefore considered preventive against colorectal cancers and improves prognosis by reducing cancer-related mortality.

Recently developed novel endoscopic technologies eliminate the limitations of conventional white-light endoscopy. The major disadvantage of conventional endoscopy relates to the difficulty in the detection of small and superficial colorectal lesions. It is reported that at least one fourth of small lesions go undetected, and 25% of these are neoplastic.[5–7] Bressler et al[8] concluded that 2–6% of all colorectal cancers are interval colorectal cancers caused by missed polyps in conventional colonoscopy. American Society for Gastrointestinal Endoscopy (ASGE) endorses the use of novel endoscopic techniques that may improve cancer detection rates.[9] One such technology, FICE, arithmetically reprocesses real images obtained via white-light endoscopy and virtual optical filters and transforms them into simultaneously developed images.[5] The detection of flat lesions and better examination of vascular and surface patterns enable the excision of these lesions and better endoscopic diagnosis.

Previously known as diminutive, nonpolypoid, or serrated lesions, small and surface lesions were named flat adeno-

mas by Muto et al.[10] Later, the term flat lesion was popularized, particularly in Japanese studies, and entered the Western literature as well. Endoscopists and histopathologists gathered in Paris to decide on a common terminology, and they published the Paris classification for flat lesions.[11]

The true prevalence of flat adenomas is not clear as these lesions easily go undetected in endoscopy. The literature states that 7–22% of polypectomies have a flat-lesion structure.[12,13] Jaramillo et al[14] reported 3% adenocarcinoma development from flat lesions. The starting series of Muto et al with 35 lesions revealed 40% of dysplasia in flat lesions.[10] Even though endoscopic polypectomy is preventive against cancer, it has high complication rates and histopathologic examination costs. In this study, we investigated the diagnosis of flat lesions, which are colorectal cancer precursors, via the FICE endoscopy system and in vivo histologic diagnostic estimations of flat lesions. Accurate in vivo histologic diagnostic estimations can reduce the complications and costs associated with unnecessary polypectomy.[15]

MATERIALS AND METHODS

This prospective study was conducted in patients who presented to the endoscopy unit of Bakirköy Dr. Sadi Konuk Training and Research Hospital from January 1st, 2015 through October 31st, 2016 for colonoscopy and who agreed to participate in the study. The study was conducted by 5 experienced endoscopists who perform more than 200 colonoscopies each, annually. Permission for the study was obtained from the local ethics board. All procedures performed in the study involving human participants were in accordance with the 1964 Declaration of Helsinki.

The study investigated flat lesion detection and diagnostic abilities of the FICE endoscopy system. Endoscopic and histopathologic data pertaining to 217 flat lesions from the 117 patients included in the study were assessed. Patients' demographic data, localization of flat lesions, flat lesion–polyp concomitancy rates, distribution of flat lesion subtypes according to the Paris and Kudo pit pattern classifications, the correlation between the endoscopic diagnostic estimations, and the pathology results of flat lesions were assessed. The positive predictive value (PPV), negative predictive value (NPV), specificity, sensitivity, and accuracy of in vivo endoscopic diagnostic estimations made of flat lesions with FICE were studied.

Study Population

Patients aged from 18 to 90 and referred to our endoscopy unit for outpatient colonoscopy for complaints or for screening purposes from January 2015 through October 2016 were considered eligible to take part in the study. Exclusion criteria included previous surgical resection of any part of the gastrointestinal tract, a history of gastrointestinal tract cancer, a history of inflammatory bowel disease, use of antiplatelet agents or anticoagulants that precluded the removal of the gastrointestinal tract polyps, poor general condition or any other reason to avoid a prolonged procedure, history of polyposis syndrome or hereditary nonpolyposis colon cancer, or the inability to give informed consent. Patients in whom the cecum or terminal ileum could not be intubated and in whom bowel preparation was inadequate were excluded as well.

Study Procedure

Procedures were performed with conscious sedation (intravenous midazolam+meperidine). The endoscopies were performed by 1 of 5 experienced endoscopists who used Fujinon endoscopes (Fujinon, Inc., Tokyo, Japan). the cecum and terminal ileum were reached with white-light guidance. After cecal intubation, the localization, size, and morphology of each flat lesion and polyp were documented during the withdrawal phase. Once a flat lesion and polyp were detected, the FICE optical system was switched on by the use of a button on the head of the endoscope. All polyps were classified according to Kudo's Pit Pattern Classification[16] and the Paris Classification.[11] During the study, withdrawal times were targeted to have a mean of at least 10 min. Flat lesion size was measured with the help of the diameter of the snare in use or the diameter of an open forceps. Lesions with a height of 3 mm or less and superficial lesions were considered to be flat lesions. All flat lesions were removed endoscopically with the help of a snare or forceps and sent for histopathologic examination. Lesion localizations up to the splenic flexure were considered left localization, and those proximal to the splenic flexure were considered right localization.

Polyp Description

Flat lesions were categorized based on their endoscopic measurement by comparing their dimensions with the known diameter of open forceps or the diameter of the snare. Lesions with a height less than 3 mm were considered to be flat lesions and were classified morphologically according to the Paris Classification. Each lesion was re-

moved separately for histopathologic examination. All detected lesions were removed and classified as neoplastic (Kudo Pit Pattern Type III, IV, V) or nonneoplastic (Kudo Pit Pattern Type II).[5]

Paris Classification

According to the Paris Classification, type 0 lesions are classified in 3 distinct groups (**Figure 1**): (1) type 0-I, polypoid; (2) type 0-II, nonpolypoid and nonexcavated; and (3) type 0-III, nonpolypoid with a frank ulcer.

Subgroups 1 and 2 were subdivided. Type 0-I includes two variants: pedunculated (0-Ip) and sessile (0-Is).

Type 0-II includes 3 variants: (1) slightly elevated (0-IIa) (**Figure 2A** and **B**); (2) completely flat (0-IIb) (**Figure 3A** and **B**); and (3) slightly depressed without ulcer (0-IIc) (**Figure 4A** and **B**).

The Modified Kudo Pit Pattern Classification

Specific mucosal pit patterns (Kudo classification) distinguished nonneoplastic from neoplastic colonic mucosal lesions. Pit Pattern 1 (round pits) and 2 (stellar or papillary pits) were associated with nonneoplastic lesions, whereas 3 (tubular pits), 4 (branchlike or gyruslike pits), and 5 (nonstructural pits) predicted neoplastic lesions, including intramucosal cancer[1,5] (**Table 1**).

Flexible Spectral Imaging Color Enhancement

FICE, also known as Fujinon intelligent chromoendoscopy, improves the visualization of mucosal structures and microcirculation by the selection of spectral transmission with a dedicated wave length. It emits and captures the entire white-light spectrum without the use of any optical filters. After light capture, digital software–based computer algorithms modify the captured images. Certain combinations of wavelengths are selectively enhanced, which results in improved visualization of subtle mucosal surface changes, especially of mucosal vessels and pit patterns The FICE systems come with 10 presets that can be customized and configured from a large number of

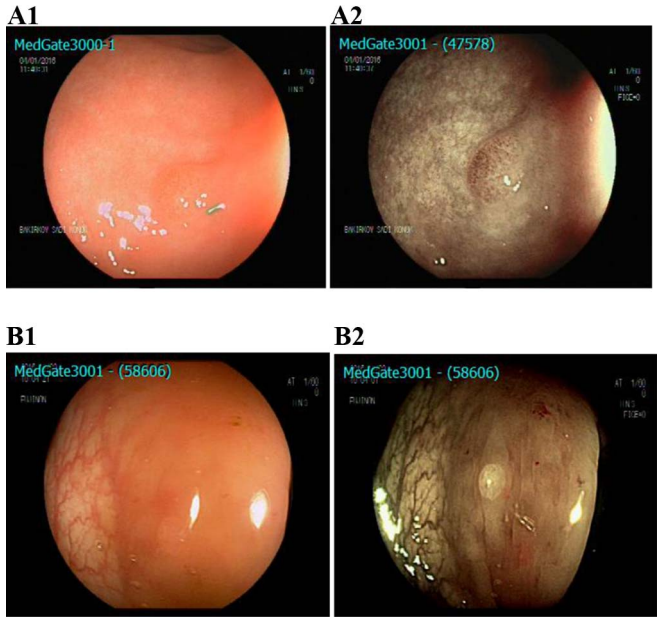

Figure 2. (**A**) Paris type 0-IIa. (A1) White light image. (A2) FICE image of the same lesion. (**B**) Paris type 0-IIa. (B1) White light image. (B2) FICE image of the same lesion.

wavelength permutations. Endoscopists can select spectral images at visible wavelengths between 400 and 695 nm, and this can be activated by a switch on the "head" of the endoscope.[5,17]

Bowel preparation was evaluated and graded as described in previous studies.[5,18] There were 4 categories of bowel preparation: excellent, good, fair, and inadequate. Colonoscopy preparation was considered inadequate when <90% of the mucosa could be seen. The patients with inadequate preparation were excluded from the study.

Statistical Analysis

Statistical analysis was conducted using JMP software version 10.0.0 (SAS, Cary, NC). Patient characteristics were analyzed via descriptive statistics. The mean and standard derivation or median and range were calculated for continuous variables. For categorical variables, the numbers

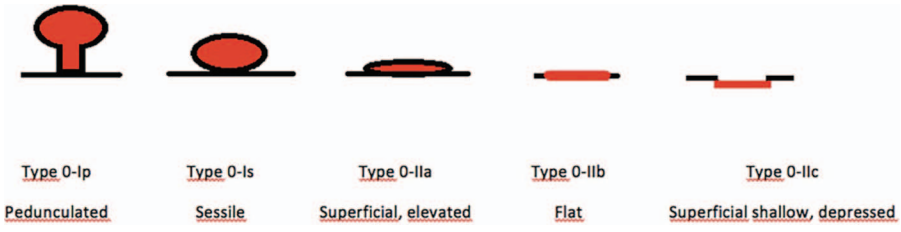

Figure 1. Paris classification.

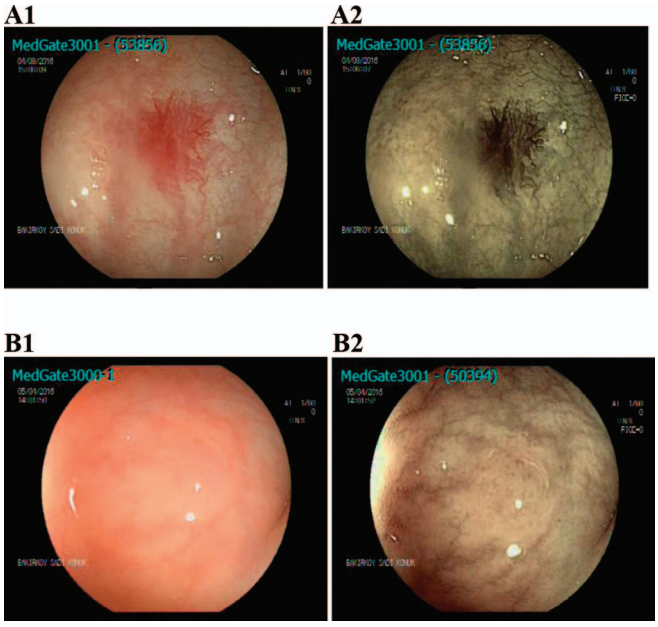

Figure 3. (**A**) Paris type 0-IIb. (A1) White light image. (A2) FICE image of the same lesion. (**B**) Paris type 0-IIb. (B1) White light image. (B2) FICE image of the same lesion.

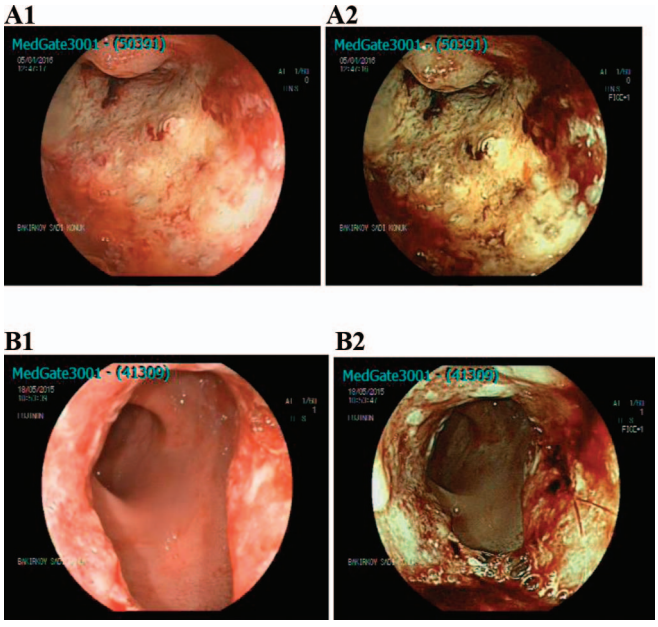

Figure 4. (**A**) Paris type 0-IIc. (A1) White light image. (A2) FICE image of the same lesion. (**B**) Paris type 0-IIc. (B1) White light image. (B2) FICE image of the same lesion.

and percentages in each category were recorded. The χ^2 test was used to compare frequency distributions. True-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) values for these endoscopic modalities were determined by using 2 × 2 tables. The diagnostic value was also measured in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. All results reaching $P < 0.05$ were considered statistically significant, and all of the performed tests were 2-sided.

Table 1.
The Modified Kudo Pit Pattern Classification

Type	Description
1	Normal round
2	Stella or papillary
3S	Tubular or round; smaller than pit type 1
3L	Tubular/large
4	Sulcus/gyrus
5	Irregular arrangement, with size equal to grade 3L, 3S, or 4

RESULTS

A total of 137 patients were included in the study, 82 of whom were male. Mean age was 58 (26–83) years. A total of 217 flat lesions were identified.

All flat lesions were classified regarding their morphology as group 0-IIa, 0-IIb, and 0-IIc according to the Paris classification system (**Table 2**). Of the lesions, 186 were group 0-IIa, 28 group 0-IIb, and 3 group 0-IIc.

The flat lesions detected were assessed endoscopically based on Kudo's pit pattern classification. Kudo 2 lesions were considered benign, and Kudo 3-4-5 lesions were considered potentially malignant because if their adenomatous structure. Class 3 lesions comprised 59.4% of all lesions (**Table 3**).

When the FICE diagnostic estimations of flat lesions and final pathology results were considered, PPV was 68.5%, NPV was 89.6%, sensitivity was 94.7%, specificity was 50.9%, and accuracy was 74.2% (**Table 4**).

Table 2.
The Morphological Types of Flat Lesions According to the Paris Classification

Type	n	%
0-IIa	186	85.7
0-IIb	28	12.9
0-IIc	3	1.4

Table 3.
Distribution of Flat Lesions According to Kudo's Pit Pattern Classification

Type*	n	%
2	58	26.8
3	129	59.4
4	29	13.3
5	1	0.5

* Pit pattern type 2 lesions were considered benign; pit pattern 3 to 5 lesions were considered potentially malignant.

Table 4.
Predictive Values of FICE in Flat Lesions

Diagnostic Value	%
PPV	68.5
NPV	89.6
Sensitivity	94.7
Specificity	50.9
Accuracy	74.2

Diagnostic estimation by using FICE endoscopic examination correlated significantly with the histopathology results ($P < 0.001$; **Table 5**).

Labeling the flat lesions proximal to the splenic flexure as "proximal" and those distal to the flexure as "distal" showed that 55.7% of the flat lesions were localized in the distal colon.

In line with the histopathologic examination results, the flat lesion in 1 patient was malignant (0.46%) and 36 patients (16.5%) had dysplasia.

DISCUSSION

Colorectal cancers are the second most common type of cancer in the Western world[19,20] and more than 90% of those cancers involve adenomatous polyps.[21,22] The term flat adenoma was defined and accepted as a precursor for colon cancer by Muto et al.[10] These lesions were known by different names in different parts of the world. The Japanese Society for Cancer of the Colon and Rectum defined flat adenomas as polyps with a diameter at least twice the height of the lesion. Later, the Paris conference established the Paris Classification to develop a common terminology for polyps, according to which flat adenomas were classified as slightly elevated (IIa), flat (IIb), and slightly depressed (IIc).[11]

Table 5.
Diagnostic Correlation Between Kudo Pit Pattern Types and Final Histopathology

Pit Pattern Type	Correlation		*P*
	n	%	
2	56	96.6	<0.001
3	81	62.8	
4	28	96.5	
5	1	100	
All lesions	166	76.5	

The developmental processes for flat adenomas are not yet clear. A part of them may be early-stage polypoid lesions. However, the polypoid phase is not necessary for these lesions to develop into carcinoma. The molecular anomalies in the development of flat adenomas are reported to be different from those in other adenomas.[23–25] It is also reported that high-grade dysplasia is higher and K-ras mutations are lower in flat adenomas.[26] Owen et al concluded in their study that APC gene mutation is lower in flat adenomas than in polyps.[26] Even though several studies report a more aggressive course in flat adenomas,[25,27] the National Polyp Study concluded that high-grade dysplasia and the risk for early-stage carcinoma in flat adenomas were similar to sessile and pedunculated polyps.[28] Soetikno et al[29] stated that, even though the risk of carcinoma is low in flat adenomas, the risk is 10 times higher than that posed by polyps.[29]

A hypothesis alternative to the adenomatous polyp–cancer sequence claims that flat lesions cause cancer. It has been argued that colorectal cancers developing from flat lesions cause ulcer and perforations by invading the colon wall instead of protruding into the lumen and causing obstruction. The fact that because cancerous flat lesions do not cause obstruction and reveal themselves, late findings such as tumor perforation may increase the mortality related of these tumors. This invasion pattern toward the lymphs and the vascular bed from the colon wall increases the biological significance of flat lesions. Because of this biological significance, it is vital to detect these adenomas during colonoscopy. This biological behavior may mean that flat adenomas cause metastasis in the lymphs in early stages.

Colonoscopy is the gold standard in preventing colorectal cancers.[30] Effective screening and the removal of adeno-

mas with colonoscopy reduce the incidence and mortality of colorectal cancers.[31] Even though polypectomies provide protection in between 76 and 90% of cases, colorectal cancers involving particularly the right side of the colon, which is known as an interval colorectal cancer, may still occur in people who are observed with colonoscopy.[22,32] Interval cancers may be related to rapidly progressing de novo adenomas, incomplete polypectomies, and missed flat adenomas. According to a study by Stoffel et al[33] the use of chromoendoscopy and advanced endoscopic techniques increases flat adenoma detection rates, thus lowering the incidence of colorectal cancer.

The literature reports a polyp miss rate of 22 to 30%.[6,7,34,35] As emphasized in these studies, the adenoma miss rate is associated with size, with polyps larger than 10 mm having a miss rate of 2%, those between 5 and 10 mm having a miss rate of 13%, and those smaller than 5 mm having a miss rate of 26%.[36] Detection of flat lesions is complicated further by the presence of mucus cap, bubbles, hard-to-see localizations below mucosal folds, poor colon preparation, flat lesions displaying the same color as normal mucosa in white-light endoscopy, and sizes under 1 cm.[37,38]

Flat adenomas comprise 8.5 and 12% of all adenomas detected by using standard white-light endoscopy, and these adenomas can be multiple.[39] On the other hand, of all adenomas detected with the use of chromoendoscopy, 6 to 36% are flat.[40]

The definition of interval colorectal carcinoma (CRC) and the revelation that small adenomas have a high miss risk during colonoscopy led to the emergence of alternative methods to standard white-light endoscopy. These efforts are meant to increase the sensitivity of colonoscopy. An increase in the quality of colonoscopic examination may increase protection from CRC. Chromoendoscopy also originated to increase the effectiveness of endoscopy but failed to become popular because of its experience-requiring, time-consuming, impractical use. The use of this hard to use method, chromoendoscopy, led to the emergence of the concept of in vivo optical diagnosis.

Recent years have witnessed the development of new advanced endoscopic techniques (e.g., FICE, NBI, and i-scan) known as digital chromoendoscopy or virtual chromoendoscopy, which do not require staining and are practical to use. Although these techniques were initially claimed not to change polyp miss rates, recent studies report lower adenoma miss rates with standard white-light endoscopy.[41–43] Although the literature includes many polyp-related studies with NBI, there is a limited number of studies on FICE. In a previous study at our clinic which compared the FICE and NBI methods in gastrointestinal polyps, both techniques yielded similar results. However, FICE had several advantages: clearer images compared to NBI, more practical use, and provision of 10 different polyp images.[5] Kang et al[15] found higher specificity with FICE than with NBI, particularly in the detection of non-polypoid lesions smaller than 5 mm.

This study used the FICE system to detect flat adenoma. With FICE examination, which could be initiated with the help of a single button during standard white-light endoscopy, the surface characteristics and vascular architecture of flat lesions could be developed and their in vivo optical diagnostic estimations made. When the flat lesions were classified according to Kudo's pit pattern classification, 58 were found to be type 2, 129 type 3, 29 type 4, and 1 type 5. When the endoscopic diagnostic estimations based on this classification were compared against final pathology results, FICE examination had a PPV of 68.5%, NPV of 89.6%, sensitivity of 94.7%, specificity of 50.9%, and accuracy of 74.2%. A statistically significant congruence was found between in vivo diagnostic estimations in FICE endoscopic examination and histopathologic examination results ($P < 0.001$).

Based on the Paris classification system, the 217 flat lesions in our study fell into the following classes: 186 were type IIa, 28 were type IIb, and 3 were type IIc. In line with the histopathologic examination results of flat lesions, the rate of malignancy was 0.46%, and the rate of dysplasia was 16.5%. The literature reports higher malignancy rates among Paris type IIc lesions.[26] Heavy dysplasia was detected in 2 of the 3 type IIc flat lesions in this study. Adenocarcinoma was detected in one flat adenoma classified as Paris type IIa.

The literature states that flat adenomas are more common among elderly women and mostly in the proximal colon. In contrast to the literature, 40% of the patients in the present study were women and 44.3% of all flat lesions were in the proximal colon.

The latest contemporary practice is the removal of all detected polyps. Polypectomy may cause certain complications, such as bleeding and perforation. Not only is polypectomy a time-consuming procedure in colonoscopy, but histopathologic examination is also a costly process. In addition, polypectomy increases the frequency of colonoscopies in screening programs. Recently, these complications and high costs have been under discussion. Instead of removing all polyps, the recommendation is for using advanced endoscopic techniques, making an effective in vivo examination, and not sending polyps that do not

raise suspicion for formal histopathologic examination.[44,45] Other than digital chromoendoscopy, confocal laser endomicroscopy (CLE)—another in vivo optical diagnosis technique—may be used for this purpose and may yield real-time optical biopsies. Examination may involve, not only the surface levels of adenomas, but also sections from its different layers.[46] However, CLE is a time-consuming and costly technique that requires the use of stain.

The researchers include experienced endoscopists and recommend starting colonoscopic examination with standard white-light colonoscopy instead of full FICE examination and performing cecal or ileal intubation, initiating FICE with the button for the lesions detected, and examining each lesion by comparing its surface and vascular characteristics with those of surrounding healthy mucosa. For endoscopists with adequate experience, a return with full FICE examination is also recommended. According to a study by Hoffman et al,[36] which compared polyp miss rates between a full examination with the advanced endoscopic technique of i-scan and white-light endoscopy, the former yielded a miss rate of 62.5% and the latter 30.0%.

The limitations of the present study include its having been conducted in a single center by the same endoscopists, not having looked for the optimal images among the 10 different FICE images obtained, and the different terminology and classification used by the pathologists. In addition, not having studied the same flat adenomas with endoscopic modalities other than FICE was also a limitation.

In sum, this study evaluated the detection and in vivo diagnostic estimations of flat lesions via the FICE option of wide-angle colonoscopes with high definition and magnification abilities performed by experienced endoscopists in a tertiary center. FICE helps in vivo histologic diagnosis of flat lesions, if not their detection, by developing the surface and vascular patterns of flat adenomas detected via white-light endoscopy and thus providing rich images. Larger, comparative, randomized, controlled studies involving new endoscopic technologies for the detection and in vivo diagnosis of flat lesions are needed in the future to reveal the real frequency of flat lesions and their biological significance.

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