Clin J Gastroenterol (2016) 9:175–183
DOI 10.1007/s12328-016-0658-3

CLINICAL REVIEW

The efficacy of autofluorescence imaging in the diagnosis of colorectal diseases

Kentaro Moriichi[1] · **Mikihiro Fujiya**[1] · **Toshikatsu Okumura**[1]

Received: 10 May 2016 / Accepted: 23 May 2016 / Published online: 13 June 2016

Abstract Image-enhanced endoscopy (IEE) has been developed and is applied in the clinical setting throughout the world. Most reports regarding IEE have evaluated the efficacy of narrow-band imaging (NBI) in the diagnosis of gastrointestinal disorders. Although autofluorescence imaging (AFI) is a form of IEE, its usefulness remains unclear. The present review focused on the efficacy of AFI in the diagnosis of colorectal disease, particularly neoplasia and ulcerative colitis (UC). AFI-based diagnoses are made via the subjective judgment of the color on the monitor. The efficacy of AFI in detection and differentiation in patients with colorectal neoplastic lesions remains controversial, which may be dependent on the study design and the diagnostic procedures. Although the number of the reports related to UC is very small, most suggest that AFI is effective in UC patients. AFI is distinct from other modalities in that it can quantitatively assess the lesion based on the fluorescence intensity without any morphological assessments. AFI could be useful for patients with colorectal disease.

Keywords Autofluorescence imaging (AFI) · Colorectal neoplasia · Ulcerative colitis (UC) · Colitis-associated cancer · Narrow-band imaging (NBI) · Image-enhanced endoscopy (IEE) · White light endoscopy (WLE)

✉ Kentaro Moriichi
morimori@asahikawa-med.ac.jp

[1] Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa, Hokkaido 078-8510, Japan

Introduction

Endoscopy plays an important role in the diagnosis and treatment of diseases of the gastrointestinal (GI) tract. Recently, image-enhanced endoscopy (IEE), including narrow-band imaging (NBI) and auto-fluorescence imaging (AFI), has been developed and clinically applied in the diagnosis of GI diseases [1–5]. A number of reports have revealed the efficacy of NBI in the diagnosis and assessment of GI neoplasms [6, 7]. NBI can morphologically evaluate the capillary architecture and the microvessels of the mucosal and submucosal layer [8]. In this aspect, the diagnostic ability of NBI is closely associated with the ability to recognize vascular patterns, thus the diagnostic accuracy of NBI appears to be dependent on the experience of individual endoscopists. AFI is another novel IEE technology that can capture fluorescence (500–630 nm) emitted from the fluorophores in human tissue [9, 10]. AFI can assess lesions without any morphological assessments based on the fluorescence intensity. In this regard, AFI is different from other devices, including conventional endoscopy and NBI. Although the number of reports on AFI are gradually increasing, its efficacy in diagnosing GI disorders is still poorly recognized by clinicians. This review focuses on the usefulness of AFI in the detection and evaluation of colorectal diseases.

Autofluorescence imaging technology

This device has an excitation light source that produces 442-nm light via a rotation filter, delivers it to the tissue surface, and then captures the reflection and fluorescence emitted from certain biomolecules (collagen, elastin) in the submucosal layer using two high-sensitivity charge-coupled devices (CCDs). The captured signals are respectively

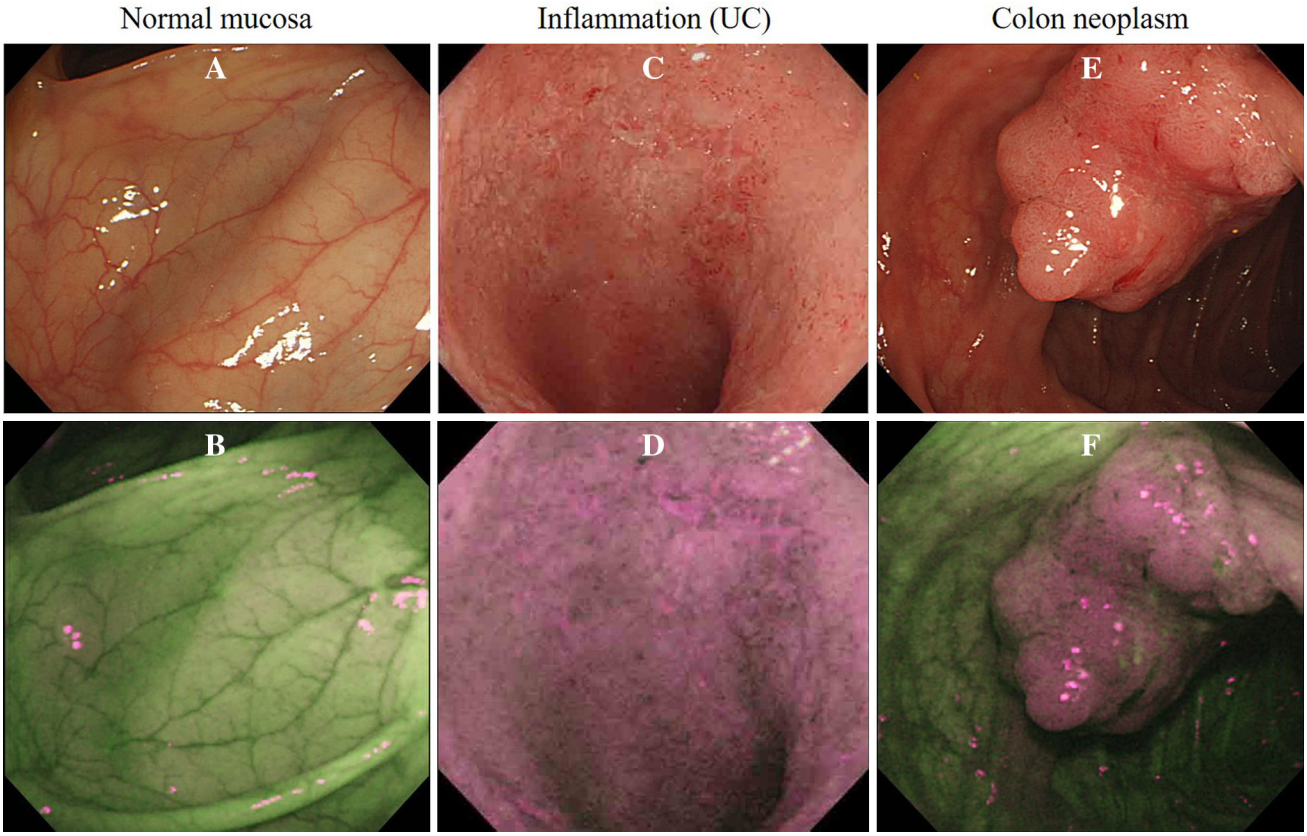

Fig. 1 The white light endoscopy (WLE) and AFI images of normal and abnormal mucosa. The normal colorectal mucosa on WLE (**a**); autofluorescence imaging (AFI) of the lesion (**b**); a WLE image of active inflammation in ulcerative colitis patient (**c**); the lesion appears *magenta* on AFI (**d**); a WLE image of colon neoplasm (**e**); the lesion appears *magenta* on AFI (**f**)

transformed into red or blue colors, and are displayed on the monitor in real-time as a color image [9, 11]. While the normal colorectal mucosa appears green, a lesion that attenuates the excitation light or the endogenous fluorophores, including thickened mucosa due to neoplasm and inflammation, will appear in magenta (Fig. 1).

Colorectal neoplasms

Colorectal cancer is one of the most common malignant tumors in Eastern and Western countries [12]. The factor that has the most influence on the survival rate of patients with colorectal cancer is the stage of cancer progression at the time of the detection [13, 14]. It is therefore important to detect early-stage cancers, such as mucosal and submucosal cancers. The detection of adenomas, which are considered to be premalignant lesions, is also important for improving the survival rate of patients with colon cancer. Several trials on endoscopic resection for colon adenoma successfully showed a decrease in the mortality of patients with colon cancer [15]. Consequently, the detection and differentiation of early-stage cancers or precancerous adenomas are essential for improving the survival rate of patients with colorectal cancer.

Detection

When using WLE, colonoscopists are thought to overlook 26–30 % of all adenomas, and 2–6 % of colon neoplasms of more than 10 mm in size [16–19], suggesting the need to develop novel efficient devices for the detection of colorectal neoplasms.

Some studies have proposed the efficacy of AFI for detecting colorectal neoplasms [10, 20–22]. Matsuda et al. reported a study in which a single experienced endoscopist conducted back-to-back colonoscopies of the right-sided colon using AFI and WLE. AFI and WLE detected 100 and 73 polyps, respectively. The miss rate for all polyps with AFI (30 %) was significantly lower than that with WLE (49 %) ($P = 0.01$) [10]. We compared the rates at which experienced and less-experienced endoscopists detected adenomas using AFI and conventional high-resolution endoscopy (HRE). Among less-experienced endoscopists (but not experienced endoscopists), AFI was found to

dramatically increase the detection rate (30.3 %) and reduce the miss rate (0 %) of colorectal adenoma in comparison to HRE (7.7, 50.0 %) [20]. McCallum et al. compared the detection rates in 54 adenomatous polyps, including 32 tubular polyps, four villous polyps, and 18 tubulovillous polyps (median size, 4 mm) using AFI and WLE. AFI could detect all polyps, while WLE missed three adenomatous polyps [21]. The results of a meta-analysis to investigate the adenoma detection rate, polyp detection rate, adenoma miss rate, and polyp miss rate from six studies suggested that AFI decreased the miss rate for both adenomas and polyps [22].

On the other hand, controversial results have also been reported [23–25]. Kuiper et al. suggested that endoscopic trimodal imaging, including AFI, did not show any improvement in comparison to standard colonoscopy in the detection of colorectal adenoma [23]. Rotondano et al. performed a prospective randomized trial (total: $n = 94$) to evaluate the detection rate of AFI for colorectal neoplasia. Among 47 patients who were first examined by AFI and then HRE, AFI detected 31 adenomas and HRE detected six additional adenomas; the detection rate was 0.66. Among 47 patients who were first examined by HRE and then AFI, AFI detected seven additional adenomas; the detection rate was 0.62. They evaluated the adenoma miss rates of AFI and HRE, which were 13 and 14.9 %, respectively [24]. Another meta-analysis investigated whether AFI could improve the adenoma detection rate in comparison to WLE and IEE (AFI and NBI), and these authors concluded that only chromoendoscopy could improve the rate [25]. The detection rate of AFI for serrated adenoma was also examined by van den Broek et al. When sessile serrated adenomas (SSAs) were included, the sensitivity decreased from 99 to 83 %, because most SSAs were detected as green areas on AFI [26].

The efficacy of AFI in the detection of colorectal neoplasms remains controversial (Table 1) because most studies on AFI have been conducted in small study populations and have been performed by a single endoscopist. In addition, the endoscopic skill of the participants appears to be another source of bias in such analyses. Further large RCTs are required to validate these results.

Characterization of colorectal lesions

Approximately 30–40 % of polyps removed by endoscopy are reported to be classified as hyperplastic polyps, which have much less potential to progress to cancer [27, 28]. The general consensus is that hyperplastic polyps are thought to be benign lesions and that they do not have neoplastic potential [21, 29–33]. It is therefore crucial to discriminate between adenomas and hyperplastic polyps before endoscopic resection to avoid labor-intensive and time-consuming procedures and the adverse events related to endoscopic resection, such as perforation.

Some reports were published to evaluate the efficacy of AFI in differentiating between neoplastic and non-neoplastic colorectal lesions (Table 2). Uedo et al. conducted a randomized cross-over trial of a total of 64 patients who underwent AFI and WLE. They evaluated 58 polyps, including 26 neoplastic polyps. The sensitivity and specificity of AFI in discriminating neoplastic from non-neoplastic polyps were 65 and 89 %, respectively [34]. Nakaniwa et al. evaluated 168 colonic polyps using AFI. An endoscopist diagnosed the lesions retrospectively. The sensitivity and specificity in differentiating adenomas and hyperplastic polyps were 89 and 81 %, respectively [35]. Van den Broek et al. reported that AFI improved the accuracy in the differential diagnosis of colon polyps, particularly for non-experienced endoscopists [36]. We conducted a prospective study and showed that AFI helped to differentiate neoplasms from hyperplastic polyps, particularly in the non-experienced endoscopists group (from 69.1 to 89.7 %) [37]. We also investigated whether AFI

Table 1 The adenoma miss rate using autofluorescence imaging and white light endoscopy

Author	Observation	Number of patients	Number of adenomas		Endoscopist	Adenoma miss rate (%)		*P* value	References
						AFI	WLE		
Matsuda	Right-sided	167	AFI → WLE	66	Single	30	49	<0.01	[10]
			WLE → AFI	95					
Moriichi	Proctosigma	88		29	Two	3.4	27.6	<0.05	[20]
Kuiper	Total	258	AFI → WLE	121	Single	28.1	33.4	NS	[23]
			WLE → AFI	112					
Rotondano	Total	94	AFI → WLE	37	Single	13	14.9	NS	[24]
			WLE → AFI	36					
Van den Broek	Total	50	AFI → WLE	40	Single	20	29	NS	[26]
			WLE → AFI	49					

AFI autofluorescence imaging, *WLE* white light endoscopy

Table 2 The diagnostic accuracy of autofluorescence imaging

Author	Number of polyps	Sensitivity (%)	Specificity (%)	PPV[††] (%)	NPV[§] (%)	Accuracy (%)	References
McCallum[†]	75	85.2	81.0	92.0	68.0	84.0	[21]
Kuiper	239	89.7	36.6	57.1	78.9	62.3	[23]
Uedo	58	65	89	95	44	71	[34]
Nakaniwa	168	88.8	81.4	93.3	71.4	86.9	[35]
Moriichi	86	94.3	68.8	93	73.3	89.5	[38]
Wanders	1152*	88.0	69.2	NA	81.5	NA	[39]
Boparai	66**	63.8	52.6	76.9	37.0	60.6	[45]

* Meta-analysis

** Including sessile serrated adenomas

[†] Quantitative evaluation

[††] Positive predictive value

[§] Negative predictive value

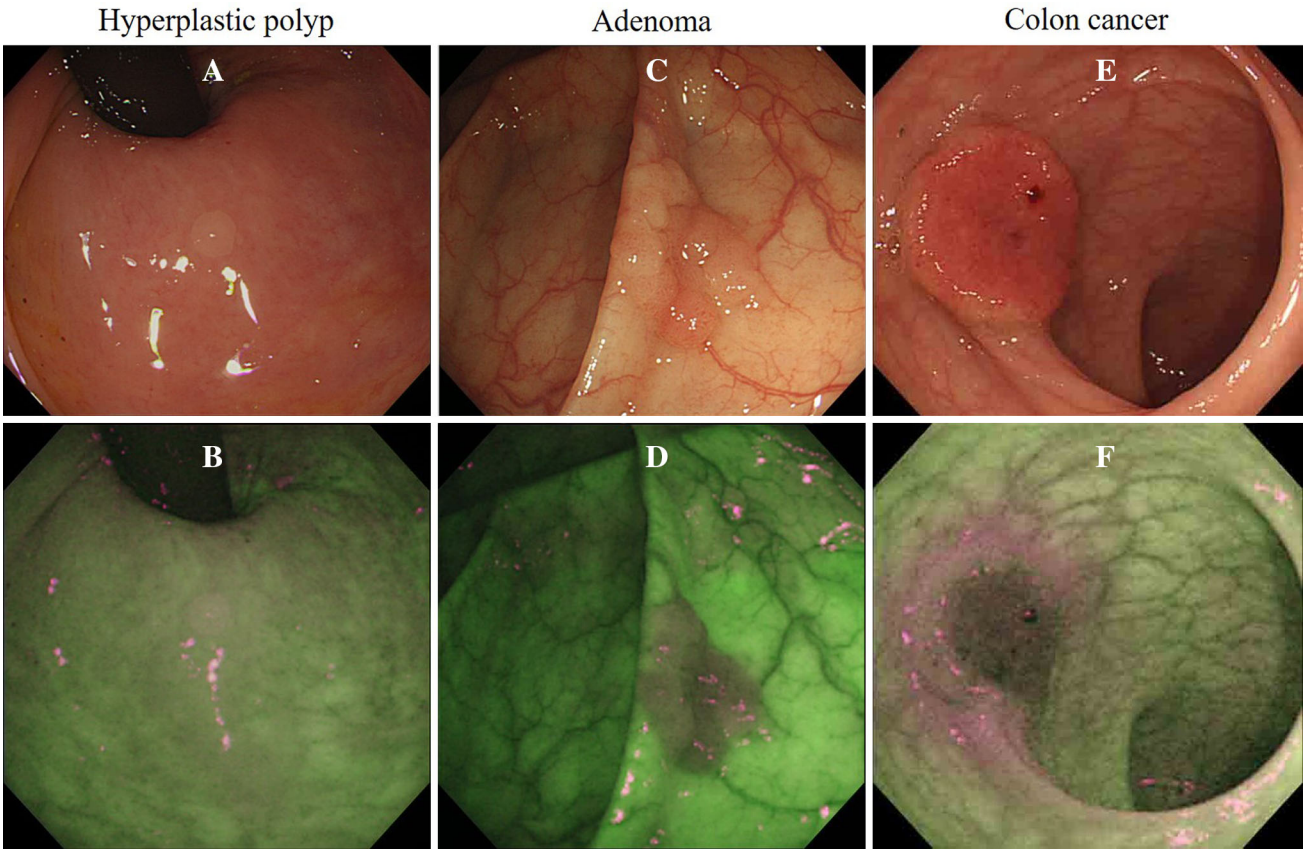

Fig. 2 The WLE and AFI images of hyperplastic polyp, adenoma, and cancer of the colon. A colonic hyperplastic polyp generally appears *green* or as a *green* lesion with a slight *magenta* spot (**a** WLE; **b** AFI), whereas adenoma (**c** WLE; **d** AFI) or cancer (**e** WLE; **f** AFI) appears *magenta* or as a magenta lesion with a *green* spot

could predict the dysplastic grade. Colorectal lesions were classified into four categories, green, green with a magenta spot, magenta with a green spot, and magenta. The intensity of the magenta component was found to increase significantly according to the grade of dysplasia. AFI is useful for predicting the dysplastic grade based on the color on the image [38] (Fig. 2).

In contrast, Wanders et al. performed a meta-analysis to evaluate the ability of various IEE modalities, including AFI, NBI, Fujinon intelligent chromoendoscopy (FICE),

i-scan (PENTAX), and confocal laser endomicroscopy (CLE), to differentiate sporadic colonic polyps. The overall sensitivity, specificity, and real-time negative predictive value of AFI in the diagnosis of adenoma were 86.7, 65.9, and 81.5 %, respectively. AFI showed good sensitivity but lower specificity than the other IEE methods [39]. Rotondano et al. reported the accuracy of AFI in the differentiation of colorectal neoplasms, AFI alone showed poor accuracy but the combined use of AFI and NBI improved the accuracy (84 %), which was superior to NBI alone ($P = 0.064$) [24]. In comparison to NBI, AFI is more accurate when the lesion is clearly detected as green or magenta. However, AFI is not useful for the diagnosis of lesions in which the color is between green and magenta [39].

Kruiper et al. reported that the sensitivity, specificity, and accuracy of NBI and AFI in differentiating adenomas from non-adenomatous lesions were 87, 63, and 75 % for NBI, and 90, 37, and 62 % for AFI, respectively. Similarly to AFI, NBI can differentiate colonic lesions with high levels of sensitivity but low levels of specificity [23].

Recently, the serrated neoplasia pathway has been recognized as another major pathway of carcinoma development (in addition to the adenoma-carcinoma pathway) [40–44]. It indicates that SSAs should be treated similarly to adenomas. Boparai et al. investigated the efficacy of AFI in the differentiation of hyperplastic polyps, SSAs, and adenomas. The sensitivity, specificity, and accuracy of AFI in differentiating between adenomas and hyperplastic polyposis syndrome (HPs) were 80, 53, and 65 %, respectively. They concluded that it was not possible to differentiate adenomas from HPs with AFI [45].

New approaches have been implemented in an attempt to improve the characterization of colorectal lesions by AFI. One of the benefits of AFI is that it quantifies the fluorescence intensity. Recently, some reports indicated the usefulness of the quantification of fluorescence intensity. McCallum et al. calculated the autofluorescence (AF) intensity ratio (AIR) for each polyp (ratio of direct polyp AF reading/background rectal AF activity). When the cutoff value was set at 2.3 (based on an ROC analysis), AF endoscopy showed a sensitivity of 85 % and a specificity of 81 % in distinguishing adenomatous polyps from hyperplastic polyps [21]. We also calculated the fluorescence intensity (F index) of 158 AF images of colorectal lesions using an image-analysis software program. High-grade adenomas showed a lower *F* index than low-grade adenomas, hyperplastic polyps, and normal mucosal tissue. However, the invasion depth in colorectal cancer patients could not be determined based on the *F* index in the AF images. The quantitative analysis of AF images using the *F* index will help to eliminate biases and facilitate the objective assessment of the utility of AFI in the diagnosis of the dysplastic grade of colonic tumors [38]. The quantification of AF images could be a method of objectively evaluating colorectal neoplasms.

Ulcerative colitis

It is well known that the chronic inflammation associated with inflammatory bowel disease (IBD) increases the risk of developing colitis-associated cancer (CAC) in patients with UC and CD [46]. The European and US guidelines recommended that regular surveillance endoscopy should be initiated from six to eight years after the first manifestation of the disease [47, 48].

Thirty-nine to 60 % of UC patients with clinical remission show high disease activity on endoscopic examinations. Such patients exhibited a high relapse rate when switching from a remission-inducing therapy to a maintenance therapy [49–51]. Thus, the endoscopic assessment of mucosal inflammation is crucial for determining the therapeutic strategy in UC patients.

The assessment of inflammation in UC patients

The assessment of mucosal inflammation in UC patients is crucial for determining a therapeutic strategy. Several reports have proposed that AFI is useful for evaluating the severity of inflammation in UC patients. We assessed the efficacy of AFI in evaluating inflammation through a comparison of the histological inflammation on AF images, particularly the quantified fluorescence intensity. The study showed that when the color purple appeared stronger on AF images, the degree of histological inflammation was more severe (Fig. 3). Furthermore, we calculated the intensity of autofluorescence (*F* index) and showed that the accuracy of AFI in predicting the active inflammation of UC lesions was 92 % when the cut-off value was set at 0.9 [52]. Osada et al. quantified each of the AFI components and found that the quantified green color was related to the Mayo endoscopic subscore (MES). They additionally identified a relationship between green and polymorphonuclear cell infiltration within MES-0 [53]. We also reported that the quantification of AFI was useful for assessing the severity of UC and that the intensity of AFI was inversely related to the histological severity. Furthermore, the quantified AFI showed a high level of accuracy and excellent inter-observer consistency [54].

Surveillance

It is often difficult to detect non-polypoid neoplasia in UC patients (Fig. 4). Previous reports have shown that at least 33 biopsy specimens or four biopsy specimens should be taken every 10 cm from all portions of the colon during

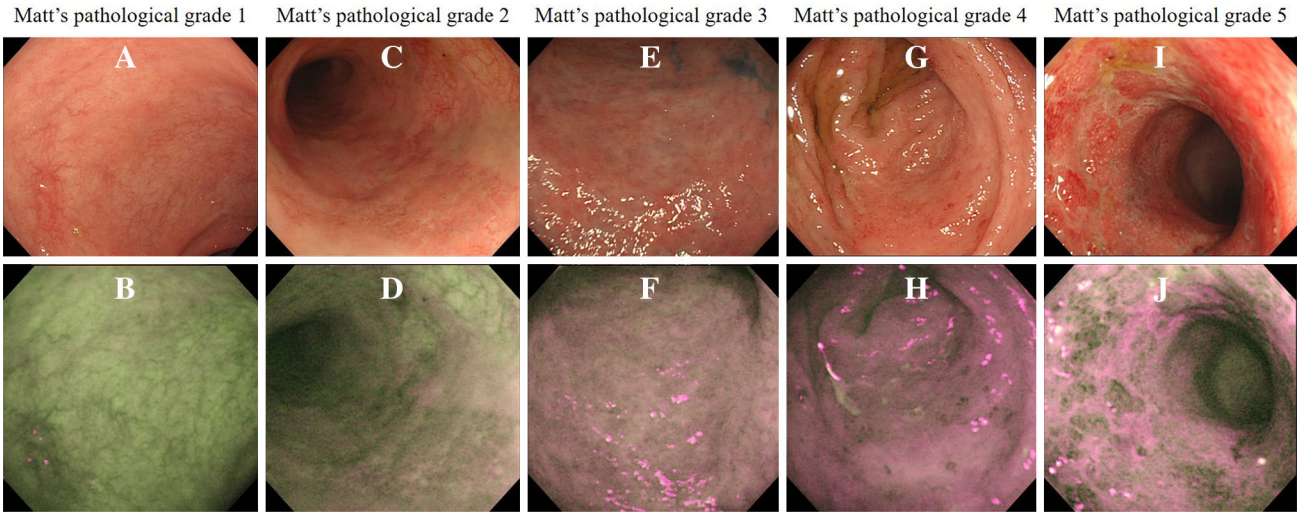

Fig. 3 The WLE and AFI images in order of the inflammation grade based on Matt's pathological criteria. Representative endoscopic images corresponding to Matt's pathological criteria. Matt's pathological grade 1 (**a** WLE; **b** AFI), 2 (**c** WLE; **d** AFI), 3 (**e** WLE; **f** AFI), 4 (**g** WLE; **h** AFI), and 5 (**i** WLE; **j** AFI)

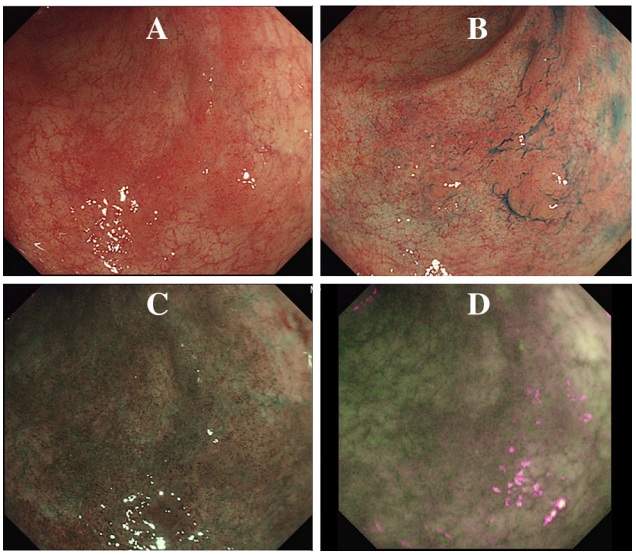

Fig. 4 The endoscopic images from a patient with colitis-associated cancer. A WLE image reveals a slightly reddish lesion in the rectum (**a**). Indigo carmine chromoendoscopy showed a flat elevated lesion (**b**). NBI detected the lesion as a slightly *brownish* area. The border of the tumor was partially unclear (**c**). The lesion appeared as a *magenta* area on AFI (**d**)

surveillance colonoscopy [55–58]. However, the standard strategy of surveillance colonoscopy seems to be associated with risks such as bleeding and lower cost-effectiveness. Several reports have indicated that chromoendoscopy with targeted mucosal biopsies was superior to the standard strategy for detecting dysplasia in IBD patients [59, 60]. Although this is a time-saving and cost-effective method, it requires the endoscopist to possess a certain skill and experience level [61].

Most reports on surveillance colonoscopy using IEE for colonic IBD (especially UC) have investigated NBI, indigo carmine chromoendoscopy and methylene blue chromoendoscopy [59, 60, 62–68]. The data available on AFI-based colitis surveillance in UC patients is limited at the present time [65, 69, 70]. Matsumoto et al. assessed 126 sites in UC patients [70]. After detecting a lesion of suspected dysplasia, such as a protruding and sharply demarcated flat mucosa with granularity by conventional endoscopy, the lesions were evaluated by AFI. The lesion was classified as high or low AFI. High AFI was defined as a lesion that was depicted as green on AFI, low AFI was defined as a lesion that was depicted as light or dark purple. Low AFI lesions showed a high incidence of dysplasia in protruding lesions, indicating that AFI may be useful in detecting dysplasia in UC patients. Van den Broek et al. performed a cross-over trial and evaluated the neoplasia miss-rates of AFI and white light endoscopy (WLE) in 50 patients with longstanding UC. In the AFI-first group ($n = 25$), AFI detected 10 neoplastic lesions and subsequent WLE detected no lesions, while WLE detected three neoplastic lesions and subsequent AFI detected three lesions in the WLE-first group ($n = 25$). They concluded that AFI improved the rate of neoplasia detection in UC patients [65].

To date, the efficacy of AFI has not been demonstrated in surveillance colonoscopy for patients with UC. Oka et al. suggested that AFI was useful for quantitatively discriminating inflammation from neoplastic lesions. Large trials are needed to elucidate the efficacy of AFI in the detection of colitis-associated dysplasia and cancer. AFI is expected to detect non-polypoid colitis-associated dysplasia and cancer without magnification [71].

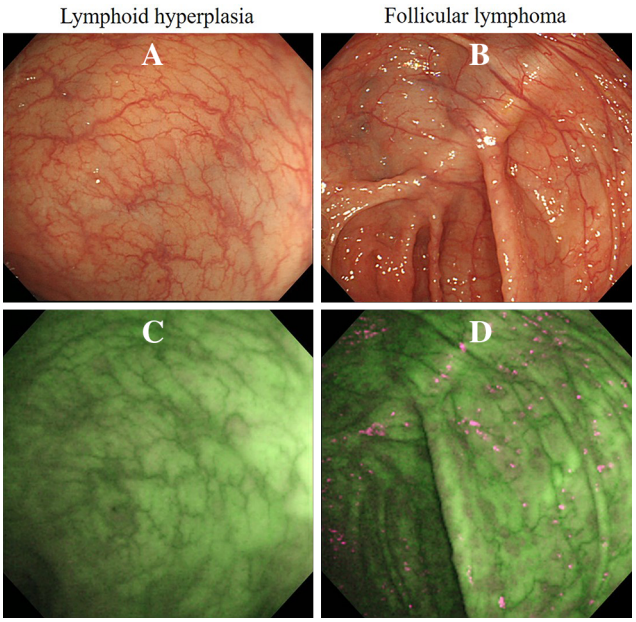

Fig. 5 The WLE and AFI of lymphoid hyperplasia and follicular lymphoma in the colon. The endoscopic images of lymphoid hyperplasia on WLE (**a**). AFI appeared as a green lesion with a slight *magenta* spot (**b**). The endoscopic images of follicular lymphoma of WLE (**c**). AFI appeared as a *magenta* lesion (**d**)

Other diseases

Lymphoma

It is important to survey GI tract lesions in patients with lymphoma. When lymphomatous lesions are detected in GI tract, the staging of the lymphoma and the therapeutic strategy might be changed. It is occasionally difficult to detect lymphomatous lesions and to differentiate lymphoid hyperplasia from lymphomatous lesions, especially in the early stage of involvement (Fig. 5). We reported a case with a small lymphomatous lesion of 7 mm in size that was detected by AFI. The lesion disappeared after chemotherapy [72]. We also investigated the usefulness of AFI in the differential diagnosis of lymphoma and lymphoid hyperplasia, using a classification system based on three predominant color intensities: green, magenta, and blended. This visual classification system showed that the overall accuracy in the diagnosis of lymphoma was 91.2 %, illustrating that AFI was useful for discriminating lymphoma from lymphoid hyperplasia [73].

Conclusion

This review focused on the efficacy of AFI in the diagnosis of colorectal disorders. AFI can quantitatively evaluate fluorescence intensity, which is completely different from conventional procedures including WLE, magnifying endoscopy, and NBI, as these assess the lesions based on morphological features. Such diagnostic morphology-based procedures require the endoscopist to possess a certain level of skill, which may lead to misdiagnosis and low inter-observer consistency. Larger-scale studies are necessary to determine the efficacy of AFI in the diagnosis of colon neoplasms and inflammatory diseases.

Compliance with ethical standards

Conflict of Interest: Kentaro Moriichi, Mikihiro Fujiya, and Toshikatsu Okumura declare that they have no conflicts of interest.

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