Autofluorescence imaging

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of new or emerging endoscopic technologies that have the potential to affect the practice of GI endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent pre-clinical and clinical studies on the topic and a MAUDE (Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but, in many cases, data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. For this review, the MEDLINE database was searched through January 2010 by using the keywords "autofluorescence imaging" and "autofluorescence endoscopy".

Reports on Emerging Technologies are drafted by one or two members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the governing board of the ASGE. These reports are scientific reviews provided solely for educational and informational purposes. Reports on Emerging Technologies are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

INTRODUCTION

Autofluorescence imaging (AFI) is based on the detection of natural tissue fluorescence emitted by endogenous molecules (fluorophores) such as collagen, flavins, and porphyrins. After excitation by a short-wavelength light source, these fluorophores emit light of longer wavelengths (fluorescence). The overall fluorescence emission differs among various tissue types due to corresponding differences in fluorophore concentration, metabolic state, and/or spatial distribution. These color differences in fluorescence emission can be captured in real-time during endoscopy and used for lesion detection or characterization.[1]

TECHNOLOGY

Autofluorescence detection was initially restricted to the use of probe-based spectroscopic devices and fiberoptic AFI endoscopes.[2,3] These latter instruments were of limited clinical value because of poor image quality related to fiberoptic technology.[4-6] Advances in image resolution, contrast, and quality were achieved recently with the development of videoendoscopic AFI systems.[7]

AFI is an integral part of trimodal imaging video endoscopes that use the red-green-blue sequential illumination platform (Table 1). Two separate monochromatic charge-coupled devices (CCDs) are located at the tip of these endoscopes for image capture. One CCD is dedicated to high-definition white-light imaging (WLI) and narrow-band imaging (NBI), whereas the other CCD is devoted to AFI. Switching from one imaging mode to another is readily achieved by a push button on the handle of the endoscope.

In AFI mode, a special rotating color filter wheel in front of the xenon light source sequentially generates blue light (390-470 nm) and green light (540-560 nm) for tissue illumination. An interference filter situated in front of the AFI CCD blocks the blue light excitation but enables tissue autofluorescence (500-630 nm) and reflected green light to filter through. The sequentially captured images of autofluorescence and green reflectance are integrated by the video processor into a real-time pseudocolor image in which normal or nondysplastic mucosa typically appears green, and dysplastic tissue appears dark purple (Fig. 1). Of note, the image algorithm (autofluorescence/green reflectance) of current AFI systems differs from that used in earlier prototype instruments in which red reflectance also contributed to the final pseudocolor image, giving a lighter purple color to abnormal mucosa.[7]

Other than prototype devices, the only commercially available AFI devices are red-green-blue–based video endoscopes with AFI capability (EVIS LUCERA SPECTRUM; Olympus Medical Systems Co, Tokyo, Japan) in Asia and Europe (Table 1). The integration of AFI technology is currently not feasible in conventional color CCD video endoscopes that are marketed for use in the United States (EVIS EXERA II, Olympus America Inc, Center Valley, Penn).

0016-5107/$36.00
doi:10.1016/j.gie.2010.11.006

TABLE 1. Endoscopes with autofluorescence imaging capability*

Feature	Gastroscope	Colonoscope
Equipment	**GIF-FQ260Z**	**CF-FH260AL/I**
Distal-end outer diameter (mm)	11	14.8
Insertion tube outer diameter (mm)	10.5	13.2
Working channel inner diameter (mm)	2.8	3.2
Bending (up/down)	210°/90°	180°/180°
Bending (left/right)	100°/100°	160°/160°
Working length (mm)	1030	1330 (I-model) 1680 (L-model)
Field of view	140°	140°
Depth of field (wide/telescope) (mm)	7-100/2-3.5	7-100/2-3
Other features	HDTV NBI Optical zoom	HDTV NBI Optical zoom

HDTV, High-definition television; *NBI,* narrow-band imaging.
*Compatible with CV-260/CLV-260SL light source and video processor (EVIS LUCERA SPECTRUM; Olympus Medical Systems Corp) not available in United States.

CLINICAL APPLICATIONS

Esophageal squamous neoplasia

AFI appears to be useful for the detection of early squamous cell carcinoma in the esophagus.[8,9] In a pilot study of 32 patients referred for the management of superficial esophageal squamous cell carcinoma, the proportion of clearly visible lesions was significantly higher with AFI than with WLI (79% vs 51%, $P < .05$).[9]

Barrett's esophagus

AFI is a sensitive but poorly specific technique for the detection of high-grade dysplasia and early cancer in Barrett's esophagus.[10-13] In a multicenter feasibility study comprising 84 patients, AFI increased the detection rate of high-grade dysplasia/early cancer from 53% to 90% relative to WLI but at the expense of a high false-positive rate of 81%. Further characterization of AFI-positive lesions with NBI reduced the false-positive rate to 26%.[12] Although AFI may be useful as an adjunctive, wide-field screening technique to WLI for identification of suspect lesions in Barrett's esophagus, AFI-positive lesions necessitate additional assessment with another modality (eg, confocal endomicroscopy or biopsy) for lesion confirmation.

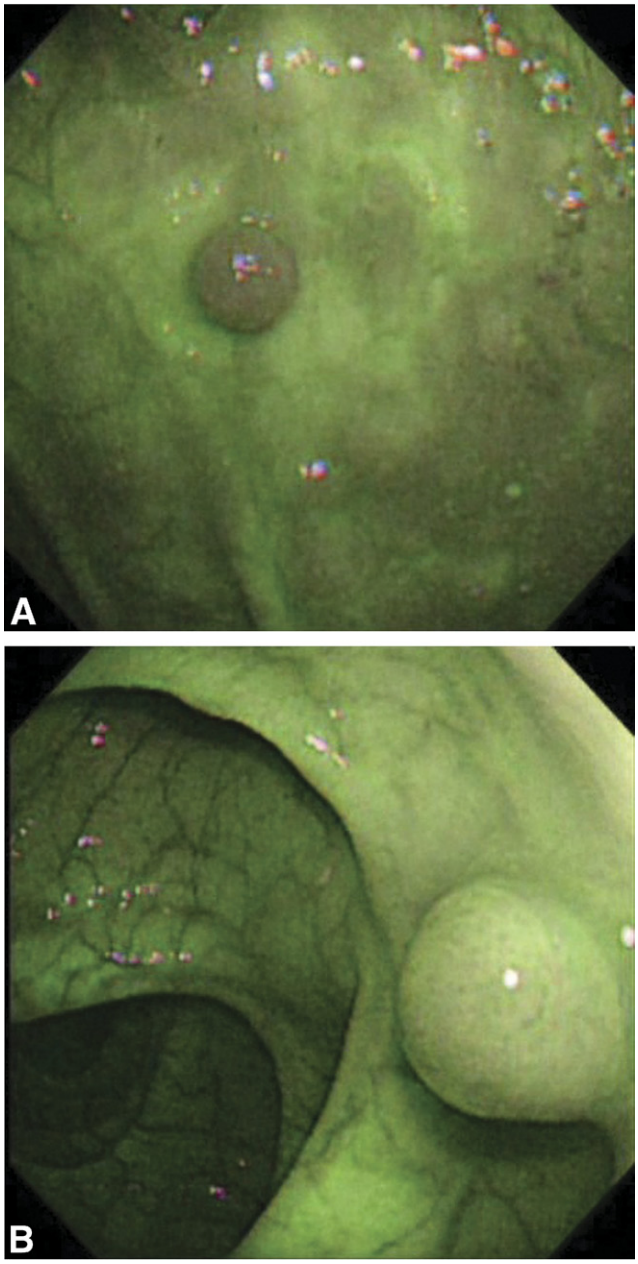

Figure 1. A, Autofluorescence imaging–negative (*green*) hyperplastic polyp. **B,** Autofluorescence imaging–positive (*dark purple*) adenoma.

Gastric neoplasia

AFI has been assessed for its role in the diagnosis of chronic atrophic fundal gastritis[14] and in the detection of early gastric cancer.[15,16] The diagnostic utility of AFI in the stomach, however, is limited by variable and inconsistent autofluorescence patterns.[17]

AFI was found to be of limited value for the detection of superficial gastric neoplasia in a prospective, comparative study comprising 91 gastric lesions in 51 patients.[15] Of the 39 biopsy-proven neoplastic lesions, 56% were diagnosed by both WLI and AFI, 18% by WLI only, and 13% by AFI only. Diagnostic sensitivities for WLI and AFI were 74%

and 64%, respectively ($P = .79$); specificities were 83% and 49%, respectively ($P < .05$).[15] In another study involving 62 patients, the addition of AFI and high-magnification NBI to WLI increased the detection rate of early gastric neoplasia by 13%. However, AFI was associated with a specificity of 24% as opposed to a specificity of 84% for WLI on a per-lesion analysis.[16] AFI is associated with a high false-positive rate for gastric lesions, which is similar to AFI findings in Barrett's esophagus.

Colon polyps

Studies evaluating AFI for colon polyp detection and/or differentiation have generated conflicting results.[18-23] In a study comprising 167 patients, assessment of the right colon was performed in a back-to-back fashion by using AFI and WLI in random order. The total number of polyps detected by AFI and WLI was 100 and 73, respectively. The miss rate for all polyps was significantly lower with AFI than with WLI (30% vs 49%, $P = .01$).[19] In contrast, AFI did not significantly reduce the adenoma miss rate compared with WLI in a randomized trial of tandem colonoscopies involving 100 patients. The adenoma miss rates for AFI and WLI were 20% and 29%, respectively ($P = .351$). The sensitivity, specificity, and accuracy of AFI for polyp differentiation were 99%, 35%, and 63%, respectively.[20]

Colon polyp differentiation with AFI was found to be unsatisfactory in a small group of patients (n = 7) with hyperplastic polyposis syndrome. The diagnostic accuracy of AFI in this study was only 65% for differentiating adenomas from hyperplastic polyps.[21] However, AFI achieved better diagnostic accuracy (77%) than WLI (57%) or NBI (63%) for polyp differentiation in the evaluation of still images by inexperienced endoscopists (accuracy compared with WLI, $P < .001$; with NBI, $P = .016$).[22] For inexperienced endoscopists, AFI features may thus be easier to interpret than NBI or WLI features as a means of polyp differentiation.

Colitis-associated neoplasia

In a randomized, comparative trial of 50 patients undergoing tandem colonoscopies, AFI improved the detection of neoplasia in chronic ulcerative colitis.[24] AFI and WLI miss rates for neoplasia were 0% and 50%, respectively ($P = .036$). The sensitivity, specificity, and accuracy of AFI for histologically proven neoplastic lesions were 100%, 42%, and 51%, respectively. False-positive lesions were mostly related to inflammation and inadequate bowel preparation.[24]

RESEARCH AGENDA

Although videoendoscopic AFI is an improvement over earlier fiberoptic systems, current image quality remains inferior to high-resolution WLI. Improvements in image resolution, noise reduction, and color contrast may be achieved by further intensifying the autofluorescence signal and by optimizing the excitation and/or detection wavelength algorithms. In addition to steady-state fluorescence detection schemes, time-resolved fluorescence imaging, which measures fluorescence decay as a function of time, may be a future method to help further enhance lesion detection. Quantitative analysis of AFI images and development of autofluorescence indices for tissue discrimination have the potential to improve diagnostic accuracy and complement, if not supplement, the visual interpretation of images.[18,25] Ultimately, autofluorescence combined with the detection of a fluorescent contrast agent that has high affinity for a targeted tissue receptor (ie, molecular beacon) may be the optimal solution for fluorescence-based diagnosis.

In addition to technological developments, randomized controlled trials are needed to assess the accuracy of AFI relative to high-definition WLI and other competing technologies, such as electronic mucosal enhancement techniques (eg, NBI, multiband imaging). Interobserver agreement and validation studies in nonenriched patient populations are also needed before AFI can be recommended for routine endoscopic practice.

SUMMARY

Although AFI may enhance lesion detection or differentiation in the GI tract, the technique currently lacks sufficient specificity to make it useful as a stand-alone diagnostic modality during endoscopic practice. AFI may be a valuable tool when used as part of a multimodal imaging scheme, but this will require further technical advances and validation in prospective, randomized trials.

DISCLOSURE

Louis-Michel Wong Kee Song disclosed receipt of research support from Olympus Corp and Fujinon Corp. David Desilets disclosed receipt of endoscopic equipment for research from Olympus America. No other financial relationships relevant to this publication were disclosed.

Abbreviations: AFI, autofluorescence imaging; CCD, charge-coupled device; NBI, narrow-band imaging; WLI, white-light imaging.

REFERENCES

1. Falk GW. Autofluorescence endoscopy. Gastrointest Endosc Clin N Am 2009;19:209-20.
2. Wong Kee Song LM, Marcon NE. Fluorescence and Raman spectroscopy. Gastrointest Endosc Clin N Am 2003;13:279-96.
3. Haringsma J, Tytgat GN, Yano H, et al. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc 2001;53:642-50.
4. Egger K, Werner M, Meining A, et al. Biopsy surveillance is still necessary in patients with Barrett's oesophagus despite new endoscopic imaging techniques. Gut 2003;52:18-23.

5. Kara MA, Smits ME, Rosmolen WD, et al. A randomized crossover study comparing light-induced fluorescence endoscopy with standard videoendoscopy for the detection of early neoplasia in Barrett's esophagus. Gastrointest Endosc 2005;61:671-8.
6. Borovicka J, Fischer J, Neuweiler J, et al. Autofluorescence endoscopy in surveillance of Barrett's esophagus: a multicenter randomized trial on diagnostic efficacy. Endoscopy 2006;38:867-72.
7. Uedo N, Iishi H, Tatsuta M, et al. A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. Gastrointest Endosc 2005;62:521-8.
8. Yoshida Y, Goda K, Tajiri H, et al. Assessment of novel endoscopic techniques for visualizing superficial esophageal squamous cell carcinoma: autofluorescence and narrow-band imaging. Dis Esophagus 2009;22: 439-46.
9. Suzuki H, Saito Y, Ikehara H, Oda I. Evaluation of visualization of squamous cell carcinoma of esophagus and pharynx using an autofluorescence imaging videoendoscope system. J Gastroenterol Hepatol 2009; 24:1834-9.
10. Kara MA, Peters FP, Ten Kate FJ, et al. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointest Endosc 2005;61:679-85.
11. Kara MA, Peters FP, Fockens P, et al. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. Gastrointest Endosc 2006;64:176-85.
12. Curvers WL, Singh R, Wong Kee Song LM, et al. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut 2008;57:167-72.
13. Curvers WL, Singh R, Wallace MB, et al. Identification of predictive factors for early neoplasia in Barrett's esophagus after autofluorescence imaging: a stepwise multicenter structured assessment. Gastrointest Endosc 2009;70:9-17.
14. Inoue T, Uedo N, Ishihara R, et al. Autofluorescence imaging videoendoscopy in the diagnosis of chronic atrophic fundal gastritis. J Gastroenterol 2010;45:45-51.
15. Kato M, Kaise M, Yonezawa J, et al. Autofluorescence endoscopy versus conventional white light endoscopy for the detection of superficial gastric neoplasia: a prospective comparative study. Endoscopy 2007;39: 937-41.
16. Kato M, Kaise M, Yonezawa J, et al. Trimodal imaging endoscopy may improve diagnostic accuracy of early gastric neoplasia: a feasibility study. Gastrointest Endosc 2009;70:899-906.
17. Kato M, Uedo N, Ishihara R, et al. Analysis of the color patterns of early gastric cancer using an autofluorescence imaging video endoscopy system. Gastric Cancer 2009;12:219-24.
18. McCallum AL, Jenkins JT, Gillen D, et al. Evaluation of autofluorescence colonoscopy for the detection and diagnosis of colonic polyps. Gastrointest Endosc 2008;68:283-90.
19. Matsuda T, Saito Y, Fu KI, et al. Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate? A pilot study. Am J Gastroenterol 2008;103:1926-32.
20. van den Broek FJ, Fockens P, Van Eeden S, et al. Clinical evaluation of endoscopic trimodal imaging for the detection and differentiation of colonic polyps. Clin Gastroenterol Hepatol 2009;7:288-95.
21. Boparai KS, van den Broek FJ, van Eeden S, et al. Hyperplastic polyposis syndrome: a pilot study for the differentiation of polyps by using high-resolution endoscopy, autofluorescence imaging, and narrow-band imaging. Gastrointest Endosc 2009;70:947-55.
22. van den Broek FJ, van Soest EJ, Naber AH, et al. Combining autofluorescence imaging and narrow-band imaging for the differentiation of adenomas from non-neoplastic colonic polyps among experienced and non-experienced endoscopists. Am J Gastroenterol 2009;104:1498-507.
23. Matsumoto T, Esaki M, Fujisawa R, et al. Chromoendoscopy, narrow-band imaging colonoscopy, and autofluorescence colonoscopy for detection of diminutive colorectal neoplasia in familial adenomatous polyposis. Dis Colon Rectum 2009;52:1160-5.
24. van den Broek FJ, Fockens P, van Eeden S, et al. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomized comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. Gut 2008;57:1083-9.
25. Aihara H, Sumiyama K, Saito S, et al. Numerical analysis of the autofluorescence intensity of neoplastic and non-neoplastic colorectal lesions by using a novel videoendoscopy system. Gastrointest Endosc 2009;69: 726-33.

Prepared by:
ASGE TECHNOLOGY COMMITTEE
Louis-Michel Wong Kee Song, MD
Subhas Banerjee, MD
David Desilets, MD, PhD
David L. Diehl, MD
Francis A. Farraye, MD, MSc
Vivek Kaul, MD
Sripathi R. Kethu, MD
Richard S. Kwon, MD
Petar Mamula, MD, NASPGHAN representative
Marcos C. Pedrosa, MD, MPH
Sarah A. Rodriguez, MD
William M. Tierney, MD, Committee Chair
This document is a product of the ASGE Technology Assessment Committee. This document was reviewed and approved by the governing board of the ASGE.