Original Research Article

Research Progress of Autofluorescence Imaging Technology in the Diagnosis of Early Gastrointestinal Tumors

Cancer Control
Volume 28: 1–7

DOI: 10.1177/10732748211044337
journals.sagepub.com/home/ccx
SAGE

Yiliang Bi, MS[1], Min Min, MD, PhD[1], Yinshu Cui, MS[2], Yuanyuan Xu, MS[2], and Xiaosong Li, MD, PhD[2]

Abstract

Early diagnosis and early treatment of gastrointestinal tumors are helpful to improve the prognosis of patients. Endoscopy is the best method for the diagnosis of early gastrointestinal tumors, but some early flat tumors may be missed under conventional white-light endoscopy. In order to improve the accuracy of endoscopic diagnosis of gastrointestinal tumors, especially early flat tumors, endoscopic autofluorescence imaging (AFI) as a new technique has been widely used in clinics in recent years. This article reviews the progress of the clinical application of AFI in the diagnosis of various gastrointestinal tumors.

Keywords

gastrointestinal tumors, autofluorescence imaging, diagnosis

Gastrointestinal tumors are relatively common, which demands the continuous improvement of diagnostic technology to make an early diagnosis and increase the detection rate of early tumors, thus further improving survival rate. Although conventional white-light electronic endoscopy system has made great progress in image clarity, resolution, and other aspects, its diagnosis still needs observation by naked eye under light irradiation and often misses atypical or minor lesions. The application of autofluorescence imaging (AFI) technology can effectively make up for the above shortcomings. Studies have shown that endoscopic AFI contributes to distinguishing normal mucosa from gastrointestinal tissue lesions, thus improving the detection rate of intraepithelial neoplasia and early tumors.[1] This article reviews the clinical application status and development prospects of AFI technology in gastrointestinal tumors.

Principle of AFI Technology

Cells and matrix of biological tissue contain many molecules, such as amino acids, porphyrins, structural proteins, etc., which can generate autofluorescence radiation signals corresponding to their absorption spectra under a certain wavelength of excitation light. This fluorescence phenomenon exists inherently in the human body and does not depend on any exogenous substance, so it is called "autofluorescence." Under the irradiation of excitation light, various kinds of endogenous fluorescence particles in biological tissue can produce autofluorescence radiation. Through the collection and processing of transducer, the autofluorescence will show unique fluorescence images or spectrum. Biochemical characteristics and morphological structures of human tissue as well as the absorption and scattering of human tissue will affect the color and fluorescence spectrum curve of the fluorescence image. According to the study of molecular biology, the transformation from normal cells to malignant cells undergoes many steps. In this process, the surrounding

[1]Department of Gastroenterology, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China
[2]Department of Oncology, The Seventh Medical Center of Chinese PLA General Hospital, Beijing, China

Corresponding Author:
Xiaosong Li, Department of Oncology, The Seventh Medical Center of Chinese PLA General Hospital, 5 Nanmencang Road, Beijing 100700, China.
Email: lixiaosong@hotmail.com

biochemical environment will generate qualitative changes, such as the concentration of endogenous fluorescent groups, mucous membrane thickness, microvascular distribution, and blood concentration. Therefore, we can distinguish normal tissues from abnormal tissues at different stages according to the differences in autofluorescence images or spectral signals of different tissues.[2,3] Policard et al. reported as early as 1924 that tumor tissues in vitro could emit fluorescence under ultraviolet radiation. After that, biologists began to study the fluorescence of various molecules in cells, proving that the fluorescence properties of various molecules were related to their physicochemical properties.[4,5]

When light irradiates on molecules that make up the human digestive tract, part of the light energy is reflected or diffused, while the remaining light energy is absorbed by molecules, and the energy state of these molecules changes from basic to high vibrational energy. This process is called excitation. Fluorophore in human digestive tract includes collagen (which makes up the basement membrane and submucosa), the reduced form of nicotinamide adenine dinucleotide (NADH), and flavin adenine dinucleotide (FAD), which mainly exist in gland cell mitochondria, lysosomal particles, and erythrocyte porphyrin.[6] If energy releases in the form of photons, then fluorescence will be emitted. In the human body, autofluorescence generation mainly depends on the excitation of some biological molecules of human tissues, such as porphyrin, collagen, amino acid, elastin, and vitamin.[7] The technique of AFI imaging is from the Olympus company.[8] Under the irradiation of short-wavelength light (blue light), the inner fluorophore in the digestive tract (mainly collagen distributed in the submucosa) is excited and emits fluorescence of longer wavelength than the blue light dose,[9] and because tumor lesions often show focal mucosal thickening and angiogenesis, autofluorescence excited by lesions is weaker than that of normal tissues, and the color of these lesions is magenta under AFI; on the other hand, the color of normal mucosal tissue around tumor lesions is green.[10] AFI can diagnose tumor lesions by comparing these 2 distinct hues. Therefore, the application of this technique may be helpful to improve the accuracy of endoscopy in diagnosing gastrointestinal tumors, especially early flat tumors. Because of the difference in molecular structure between normal tissue and cancerous tissue, the characteristics of fluorescence spectrum between these 2 tissues are also different. On the basis of this feature, AFI technology could distinguish normal tissue from cancerous tissue, thus making the diagnosis of early tumor.

Characteristics of AFI Technology

The principle of AFI technology is based on different fluorescence spectra generated by different chemical compositions between tumor tissue and its surrounding normal tissue under the irradiation of a certain wavelength of light. This technology does not need any auxiliary drugs; therefore, it can avoid human cell injuries induced by additional drugs and can also avoid patients' inconvenience due to taking drugs. In the AFI endoscopic mode, normal tissue shows light green, tumor tissue shows red, and deep blood vessels show dark green. AFI endoscopy is superior to white-light endoscopy in discovering precancerous lesions and early tumors. Therefore, the combination of AFI technology and the endoscopic system has an irreplaceable place for the diagnosis of early gastrointestinal tumors. However, AFI endoscopy also has some limitations. The problem appears to be the small specificity of the method and the large number of false positive results. This was due to the nature of AFI, which is based on changes in abnormal tissues, leading to a change in the scattering, reflectance, and absorption of ultraviolet and visible light. The results were affected by the presence of inflammation, excessive tissue congestion, tissue fragility, and the resulting bleeding. Further improvement of AFI systems is necessary, such as allowing for the elimination of the hemoglobin absorption spectrum.[11,12] Although AFI endoscopy is sensitive to autofluorescence produced by tissue, such as normal or cancerous tissue, it remains not as good as the narrow band imaging (NBI) technique in terms of observing submucosal vessels and mucosal morphology. In addition, the image quality of AFI endoscopy is often affected by some confounding factors and needs to be further improved.[13] Third, the AFI colonoscope is thicker and is more difficult for insertion in patients who have undergone colorectal resection or major abdominal surgery at high-volume colonoscopy centers than the usual colonoscope (white-light imaging, WLI).[14] Fourth, AFI using the "red flag" technique, may be useful in the characterization of small colonic polyps, however, with 1 recent study reporting sensitivity, specificity, and accuracy of 97%, 56%, and 74%, respectively, in the hands of experienced colonoscopists.[2] Fifth, for beginners, it is much different from the white-light image, which is more difficult to adapt than the NBI image.[13] Finally, AFI is relatively more expensive than WLI.[13]

Search Strategy and Criteria

The PubMed database was searched for articles published prior to Aug 07, 2020, using the keywords (autofluorescence imaging or AFI) and/or (white-light imaging or WLI) and "esophageal tumor" or "colorectal carcinoma" or "gastric cancer." A total of 1819 articles were identified, finally, 185 of which were consistent with our criteria. The flowchart illustrating the search strategy for identifying related studies is shown in Figure 1. 30 articles were about clinical trials or randomized controlled trials for esophageal tumor, 39 were about gastric cancer, and 116 were about colorectal carcinoma. We reviewed all the above articles and summarized the

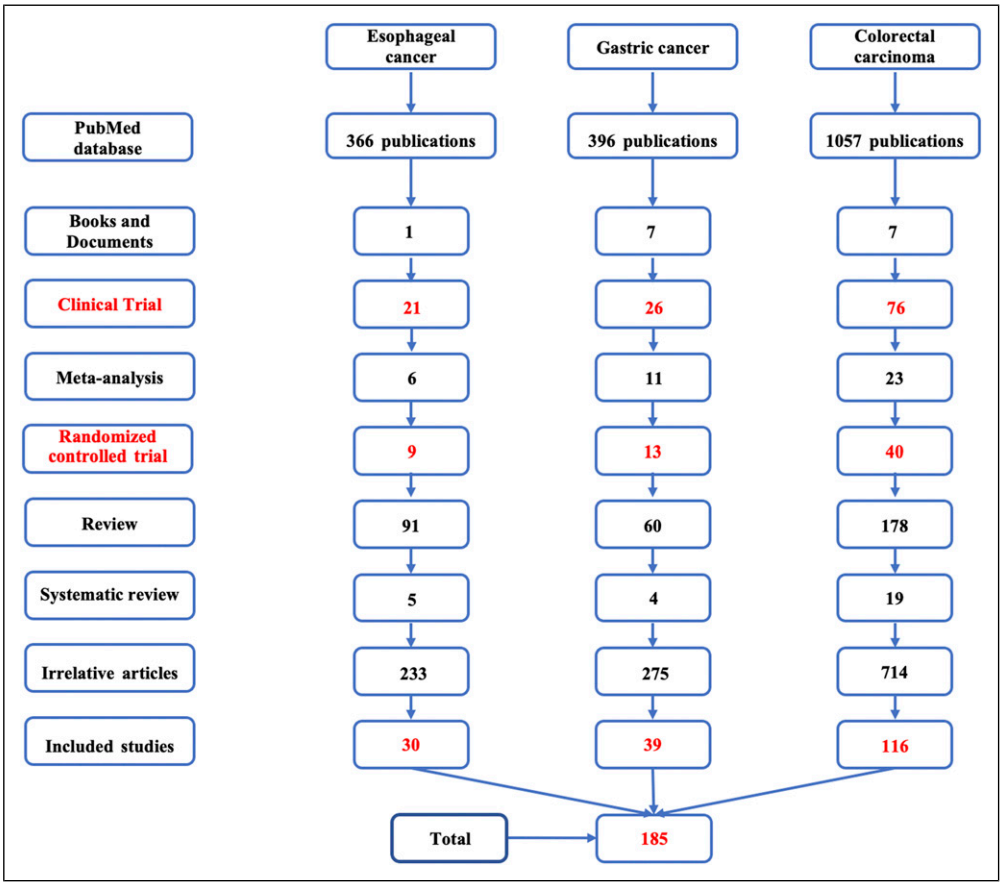

Figure 1. The flowchart illustrating the search strategy for identifying related studies.

advantages for AFI, rather than WLI in gastrointestinal tumors. The following information was shown the results in each type of gastrointestinal tumors.

Application of AFI in Early Esophageal Tumor

Esophageal tumor has become one of the malignant tumors with a rapidly increasing incidence in recent decades. The fatality rate of esophageal tumor in China ranks first in the world.[15,16] Early esophageal tumor refers to those whose cancer tissues are confined to esophageal mucosa or submucosa and do not reach the muscular layer.[17] In recent years, clinical studies have shown that a postoperative 5-year survival rate of early esophageal tumor is more than 90%, while for patients with middle and advanced esophageal tumor, their 5-year survival rate is low, regardless of surgery, chemotherapy, or radiotherapy. Therefore, the diagnosis and treatment of early esophageal tumor and its precancerous lesions have become a priority among priorities.

Improving the early diagnosis rate of esophageal tumor is an effective method to ameliorate the effect of the prevention and treatment of esophageal tumor. A retrospective analysis of about 200 endoscopic procedures in the upper digestive tract showed that autofluorescence imaging is a sensitive method to diagnose precancerous and cancerous early stages of the diseases located in esophagus. Barrett's metaplasia was confirmed in 90% vs 79% (AFI vs WLE).[18] Holz et al[19] included 58 tissue regions of 22 patients for autofluorescence spectrum analysis and compared them with the results of pathological biopsy. Autofluorescence endoscopy has a more reliable effect in the detection of early Barrett's esophageal tumor and severe atypical hyperplasia, and its detection rate is higher than that of conventional white-light endoscopy. Endlicher et al[20] used the D-Light system and detected 10 cases of atypical hyperplasia in 47 cases of Barrett's esophagus, in which 3 cases were newly detected by the fluorescence technique. When using the D-Light system to diagnose highly atypical hyperplasia and early carcinoma in Barrett's esophagus, the fluorescence technique can reduce the number of biopsies, increase the positive rate of biopsies, and false negative rate is 0. However, for lesions with low-grade atypical hyperplasia, there is no significant difference in the detection rate between fluorescence endoscopy and conventional endoscopy.[21]

Prospective cohort studies by Uedo et al[22] and Suzuki et al[23] confirmed that AFI was significantly more sensitive than conventional white-light endoscopy in the detection and

diagnosis of early esophageal tumor. A prospective study by Kara et al[24] found that AFI could accurately diagnose esophageal severe atypical hyperplasia and early carcinoma lesions in patients with Barrett's esophagus, while these patients might be missed by conventional white-light endoscopy. However, Suzuki et al[25] used NBI and AFI technology to show 31 superficial esophageal tumor lesions in 24 patients with superficial esophageal tumor, and 3 senior gastrointestinal endoscopists examined and evaluated the imaging of lesions. And results showed that NBI could display superficial esophageal tumor lesions more clearly than AFI, but in terms of displaying superficial depressed esophageal tumor lesions with a diameter of less than 2 cm, there was no significant difference in the resolution between 2 groups. Due to the small sample size of this clinical study, the application value of AFI in the diagnosis of esophageal tumor remained unclear and needed to be further determined by large-sample clinical randomized controlled trials.

Application of AFI in Early Gastric Carcinoma

More than 50% of early gastric carcinoma showed well-defined pink lesions under AFI, while its surrounding mucosa showed a green background, which suggested that mucosa presented changes of atrophic gastritis.[26] Otani et al[27] used the principle of red-green hue contrast between lesions under AFI and its surrounding normal tissues, proposing the concept of "Green-Red ratio (G/R ratio)." And then their team performed AFI to detect 72 non-ulcerative gastric carcinoma lesions, finding that the average AF index of intramucosal carcinoma was 0.99, which was significantly different from that of submucosal carcinoma and invasive carcinoma, suggesting that AFI could be used to evaluate the depth of longitudinal invasion of gastric carcinoma. In the prospective cohort study of Tada et al.[28] endoscopists from 2 groups, that is, the senior group and less clinical experience group (5 endoscopists in each group), evaluated 50 gastric lesions (20 early cancer lesions and 30 benign lesions) by using white-light endoscopy and AFI, respectively. And results showed that AFI could significantly improve the diagnostic sensitivity of endoscopists with less clinical experience in the diagnosis of early gastric carcinoma. However, intragastric inflammation and hyperplastic lesions could also thicken mucosal layer and change local blood perfusion, thus showing contrast hubs similar to those of tumor lesions under AFI.[28] Therefore, the reliability of AFI in the clinical diagnosis of gastric carcinoma is still controversial.

Application of AFI in Early Colon Carcinoma

AFI could provide useful diagnostic information regarding preneoplastic and neoplastic colorectal lesions. The research included 188 patients with colorectal mucosal lesions diagnosed on WLE and assessed using AFI, and the results showed that the NCV significantly correlated with the histopathology results.[12] Diagnosis of small polyps is important for the prevention of colorectal cancer. Non-polypoid neoplasms are more difficult to detect than polypoid neoplasms by conventional WL colonoscopy, and some have a higher potential for malignancy. A procedural decision to avoid resection of non-neoplastic polyps would spare patients the cost and risk of a polypectomy. AFI is considered to be a feasible tool that can discriminate colon adenoma from hyperplastic polyps. A total of 183 patients undergoing AFI and NBI examinations were enrolled in a prospective multicenter study, and 339 adenomas and 85 hyperplastic polyps were identified. AFI and NBI could distinguish adenoma from hyperplastic polyps with an accuracy of 84.9 % and 88.4%, respectively. In the 358 lesions in which the AFI diagnosis was consistent with that of NBI, the accuracy, sensitivity, and specificity were high at 91.9%, 92.7%, and 92.9 %, respectively.[29] Another study showed the sensitivity, specificity, and accuracy of AFI in differentiating adenomas from nonadenomatous lesions were 90%, 37%, and 62%, respectively. AFI differentiated colonic lesions with high levels of sensitivity but low levels of specificity.[30]

At present, a large number of reports have pointed out that the diagnostic value of AFI endoscopy for colorectal precancerous lesions and early colorectal carcinoma is significantly superior to that of conventional white-light endoscopy. Takeuchi et al analyzed 404 WLI and 398 AFI to detect colorectal flat neoplasms from a prospective, multicenter, randomized controlled trial in 9 institutions. They gained a conclusion that AFI improved the detection of flat colorectal carcinoma compared with WLI (0.87 vs 0.53), whereas overall and polypoid neoplasm detection was not significantly different between the groups (1.33 vs 1.14, 0.46 vs 0.60).[14] Watanabe et al[31] examined 12 cases of early superficial colorectal carcinoma by performing fluorescence endoscopy with the AFI endoscopy system. The results showed that all the 12 cases were accurately detected by AFI, while 4 cases were missed by traditional white-light endoscopy. The study of Haringsma et al[32] also showed that the diagnostic rate of AFI endoscopy was better than that of conventional white-light endoscopy. In the cohort study of Matsuda et al,[33] 167 patients were randomly divided into 2 groups: The sequential detection of AFI–white-light endoscopy group (n = 83) and the sequential detection of white-light endoscopy–AFI group (n = 84). The results showed that AFI found 100 polyps, while white-light endoscopy found 73 polyps. The missed diagnosis rate of AFI was significantly lower than that of white-light endoscopy, so AFI was easier to detect colonic polyps than conventional white-light endoscopy. The prospective study of Ramsoekh et al[34] also used white-light endoscopy–AFI or AFI–white-light endoscopy for sequential detection, finding that AFI was more sensitive than conventional white-light endoscopy in the diagnosis of colorectal adenomas in Lynch syndrome and hereditary colorectal cancer. In a prospective

randomized controlled study conducted by Takeuchi et al.[35] 561 patients were divided into 4 groups: white-light endoscopy group (n = 133), white-light endoscopy + cap group (n = 141), AFI group (n = 147), and AFI + cap group (n = 140). The results showed that the detection rate of colorectal tumors in the AFI + cap group was significantly higher than that in the white-light endoscopy group. In addition, AFI could significantly improve the detection rate of flat colorectal tumors compared with conventional white-light endoscopy. However, another view was that it was still unclear for AFI to diagnose flat and depressed colorectal lesions; moreover, these flat or depressed lesions tended to be more malignant.[36] Inoue et al[37] examined 49 superficial colorectal carcinoma lesions by white-light endoscopy, AFI, and chromoendoscopy, respectively, and then the imaging quality was evaluated by 3 endoscopists. The results showed that the ability of AFI to identify superficial colorectal carcinoma lesions was significantly better than that of conventional white-light endoscopy and was similar to that of chromoendoscopy. While in terms of identifying the boundary of superficial colorectal carcinoma, AFI was superior to white-light endoscopy, but not as good as chromoendoscopy.

Discussion

AFI, NBI, and flexible spectral imaging color enhancement (FICE) are 3 types of image-enhanced endoscopy (IEE) carried out to diagnose gastrointestinal tumors. There are many advantages in diagnosis of neoplastic tumors, evaluation of invasion depth for cancerous lesions, and detection of neoplastic lesions.[38] In recent years, AFI technology has been increasingly applied in the clinical diagnosis of gastrointestinal tumors. Now, it is considered that AFI is highly sensitive in the diagnosis of gastrointestinal malignant tumors. Besides, AFI will have a greater advantage than conventional endoscopy in the detection of lesions with unobvious morphological features and is of great significance to improve the detection rate of early tumors. However, at present, AFI still has some limitations. Before AFI is widely accepted and used to guide the clinical diagnosis of gastrointestinal tumors, it still has some problems to be solved, such as the low resolution of endoscopic images of AFI, which makes lesions relatively vague and influences diagnosis. Gastrointestinal mucosal inflammation and proliferative lesions can also thicken the mucosal layer and show hues similar to tumor lesions under AFI, which affects the differential diagnosis of inflammatory lesions from tumor lesions. Compared with other special staining methods (such as NBI, chromoendoscopy, etc.), AFI fails to show a clear advantage in the accuracy of the diagnosis of gastrointestinal tumors. Besides, in a systematic review and meta-analysis including 13 studies compared diagnosis of sessile serrated adenomas/polyps with IEE, the results indicated that AFI showed lower sensitivity in head-to-head comparisons with WLE (56% vs 66%).[39] The AFI system has been used to enhance detection of early lesions in the esophagus, stomach, and colon. It showed that the sensitivity and specificity for identifying non-polypoid neoplasms was not significantly different between AFI and WL, while false-positive results tended to be more frequent for the AFI images than for the WL images. It is necessary for the AFI system to improve technology and resolution for the use of detection of colorectal neoplasms.[40] Finally, we were based on the results of published literature. For autofluorescence endoscopy or visualization endoscopy, only a single center or multicenter trial is carried out. Clinical observation on its sensitivity, effectiveness, and limitations still needs to be confirmed by a large sample and more multicenter clinical studies. At present, the combined application of AFI, NBI, and chromoendoscopy may be accepted as an ideal strategy for the diagnosis of gastrointestinal tumors, especially early flat tumors. Furthermore, a novel method called hyperspectral-imaging fluorescence excitation scanning (Nikon Instruments, Japan) has been reported for colon cancer detection,[41] which may offer an alternative approach for discriminating early gastrointestinal tumors and is a perfect supplement to AFI technology. The expression of recognized disease biomarkers and the heterogeneity of such expression are of paramount importance to guide lesion differentiation and targeted treatment selection. Fluorescence molecular guidance in the near-infrared spectroscopy can enhance tissue penetration and assure minimal background due to a minimization of tissue attenuation and autofluorescence by comparison with the visible, thereby, superficial and sub-surface tissue biomarkers which can be optimally visualized. However, widespread clinical use of this in colonoscopy has been limited, by both technological and translational hurdles.[42]

Conclusion

To sum up, as a novel mucosal special staining technique, AFI has made great progress in the clinical diagnosis of gastrointestinal tumors in recent years. A large number of studies have confirmed that AFI has obvious advantages over conventional white-light endoscopy in the diagnosis of gastrointestinal tumors. But at present, AFI technology still has some shortcomings and disputes in the diagnosis of gastrointestinal tumors. Besides, AFI technology and diagnosis theory still requires further improvement, which depends on more high-quality laboratory and clinical researches.

Author's Note

Yiliang Bi and Min Min contributed equally to this work

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This work was supported by grants from National Key Research and Development Program of China (No. 2018YFB0407200), National Natural Science Foundation of China (No. 61975239, 81572953) and Beijing Nova Programme Interdisciplinary Cooperation Project (No.Z191100001119140).

Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

ORCID iD

Xiaosong Li https://orcid.org/0000-0002-5731-8488

References

1. Banerjee B, Miedema B, Chandrasekhar HR. Emission spectra of colonic tissue and endogenous fluorophores. *Am J Med Sci*. 1998;316(3):220-226.
2. Borisova E, Plamenova L, Keremedchiev M, Vladimirov B, Avramov L. Endogenous and exogenous fluorescence of gastrointestinal tumors: initial clinical observations. In *Seventeenth International School on Quantum Electronics: Laser Physics and Applications*; 2013:8770.
3. Keereweer S, Van Driel PBAA, Snoeks TJA, et al. Optical image-guided cancer surgery: challenges and limitations. *Clin Canc Res*. 2013;19(14):3745-3754.
4. Levitt JM, McLaughlin-Drubin ME, Münger K, Georgakoudi I. Automated biochemical, morphological, and organizational assessment of precancerous changes from endogenous two-photon fluorescence images. *PloS One*. 2011;6(9):e24765.
5. Georgakoudi I, Quinn KP. Optical imaging using endogenous contrast to assess metabolic state. *Annu Rev Biomed Eng*. 2012; 14:351-367.
6. Aihara H, Tajiri H, Suzuki T. Application of autofluorescence endoscopy for colorectal cancer screening: rationale and an update. *Gastroenterology research and practice*. 2012;2012: 971383.
7. Monici M. Cell and tissue autofluorescence research and diagnostic applications. *Biotechnol Annu Rev*. 2005;11:227-256.
8. 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(4):521-528.
9. Dacosta RS, Wilson BC, Marcon NE. Optical techniques for the endoscopic detection of dysplastic colonic lesions. *Curr Opin Gastroenterol*. 2005;21(1):70-79.
10. 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(4):521-528.
11. Cholewka A, Stanek A, Kwiatek S, Sieroń A, Drzazga Z. Does the temperature gradient correlate with the photodynamic diagnosis parameter numerical colour value (NCV)? *Photodiagnosis Photodyn Ther*. 2013;10(1):33-38.
12. Strzelczyk N, Kwiatek S, Latos W, Sieroń A, Stanek A. Does the numerical colour value (NCV) correlate with preneoplastic and neoplastic colorectal lesions? *Photodiagnosis Photodyn Ther*. 2018;23:353-361.
13. Zhang P, Dong WG, Tang SQ. Research on System type selection of electronic endoscopy between narrow-band imaging and auto fluorescence imaging. *Chin Med Equip J*. 2011;32(01): 101-104.
14. Takeuchi Y, Sawaya M, Oka S, et al. Efficacy of autofluorescence imaging for flat neoplasm detection: A multicenter randomized controlled trial (A-FLAT trial). *Gastrointest Endosc*. 2019;89(3):460-469.
15. Sweed MR, Edmonson D, Cohen SJ. Tumors of the esophagus, gastroesophageal junction, and stomach. *Semin Oncol Nurs*. 2009;25(1):61-75.
16. Wani S, Puli SR, Shaheen NJ, et al. Esophageal adenocarcinoma in barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. *Am J Gastroenterol*. 2009; 104(2):502-513.
17. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part I. *Esophagus*. 2017;14(1):1-36.
18. Sieroń-Stołtny K, Kwiatek S, Latos W, et al. Autofluorescence endoscopy with "real-time" digital image processing in differential diagnostics of selected benign and malignant lesions in the oesophagus. *Photodiagnosis Photodyn Ther*. 2012;9(1): 5-10.
19. Holz JA, Boerwinkel DF, Meijer SL, et al. Optimized endoscopic autofluorescence spectroscopy for the identification of premalignant lesions in Barrett's oesophagus. *Eur J Gastroenterol Hepatol*. 2013;25(12):1442-1449.
20. Endlicher E. Endoscopic fluorescence detection of low and high grade dysplasia in Barrett's oesophagus using systemic or local 5-aminolaevulinic acid sensitisation. *Gut*. 2001;48(3):314-319.
21. Ell C. Session C: CNS tumors (Abstract Nos. C1-C14). *Ann Oncol*. 2003;14(suppl 4Suppl 4):430-433.
22. 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(4):521-528.
23. 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(12):1834-1839.
24. Kara MA, Peters FP, Ten Kate FJW, Van Deventer SJ, Fockens P, Bergman JJGHM. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. *Gastrointest Endosc*. 2005;61(6):679-685.
25. Suzuki H, Saito Y, Oda I, Kikuchi T, Kiriyama S, Fukunaga S. Comparison of narrowband imaging with autofluorescence imaging for endoscopic visualization of superficial squamous cell carcinoma lesions of the esophagus. *Diagn Ther Endosc*. 2012;2012:507597.
26. 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(4):219-224.

27. Otani A, Amano Y, Koshino K, et al. Is autofluorescence imaging endoscopy useful for determining the depth of invasion in gastric cancer? *Digestion*. 2010;81(2):96-103.
28. Tada K, Oda I, Yokoi C, et al. Pilot study on clinical effectiveness of autofluorescence imaging for early gastric cancer diagnosis by less experienced endoscopists. *Diagn Ther Endosc*. 2011;2011:419136.
29. Sato R, Fujiya M, Watari J, et al. The diagnostic accuracy of high-resolution endoscopy, autofluorescence imaging and narrow-band imaging for differentially diagnosing colon adenoma. *Endoscopy*. 2011;43(10):862-868.
30. Kuiper T, van den Broek FJC, Naber AH, et al. Endoscopic trimodal imaging detects colonic neoplasia as well as standard video endoscopy. *Gastroenterology*. 2011;140(7): 1887-1894.
31. Watanabe H, Ogihara T, Namihisa A, et al. Real-time diagnosis of superficial type early colorectal cancers using an autofluores-cence endoscopic system. *Gastrointest Endosc*. 1998;47:AB41.
32. Haringsma J, Tytgat GNJ. Light-induced fluorescence endosopy (life) for the in vivo detection of colorectal dysplasia. *Gastroenterology*. 1998;114:A606.
33. Matsuda T, Saito Y, Fu K-I, et al. Does Autofluorescence Imaging Videoendoscopy System Improve the Colonoscopic Polyp Detection Rate?-A Pilot Study. *Am J Gastroenterol*. 2008; 103(8):1926-1932.
34. Ramsoekh D, Haringsma J, Poley JW, et al. A back-to-back comparison of white light video endoscopy with autofluorescence endoscopy for adenoma detection in high-risk subjects. *Gut*. 2010;59(6):785-793.
35. Takeuchi Y, Inoue T, Hanaoka N, et al. Autofluorescence imaging with a transparent hood for detection of colorectal neoplasms: a prospective, randomized trial. *Gastrointest Endosc*. 2010;72(5):1006-1013.
36. Aihara H, Tajiri H, Suzuki T. Application of autofluorescence endoscopy for colorectal cancer screening: rationale and an update. *Gastroenterology research and practice*. 2012;2012: 971383.
37. Inoue K, Wakabayashi N, Morimoto Y, et al. Evaluation of autofluorescence colonoscopy for diagnosis of superficial colorectal neoplastic lesions. *Int J Colorectal Dis*. 2010;25(7): 811-816.
38. Yoshida N, Yagi N, Yanagisawa A, Naito Y. Image-enhanced endoscopy for diagnosis of colorectal tumors in view of endoscopic treatment. *World J Gastrointest Endosc*. 2012;4(12): 545-555.
39. Parikh ND, Chaptini L, Njei B, Laine L. Diagnosis of sessile serrated adenomas/polyps with image-enhanced endoscopy: A systematic review and meta-analysis. *Endoscopy*. 2016;48(8): 731-739.
40. Odagaki T, Sakamoto T, Sekiguchi M, et al. What is the accuracy of autofluorescence imaging in identifying non-polypoid colorectal neoplastic lesions when reviewed by trainees? A pilot study. *Dig Endosc*. 2013;25(4):428-433.
41. Leavesley SJ, Walters M, Lopez C, et al. Hyperspectral imaging fluorescence excitation scanning for colon cancer detection. *J Biomed Opt*. 2016;21(10):104003.
42. Garcia-Allende PB, Glatz J, Koch M, et al. Towards clinically translatable NIR fluorescence molecular guidance for colonoscopy. *Biomed Opt Express*. 2013;5(1):78-92.