



# Advanced endoscopic imaging: a narrative review

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**Objective:** The aim of this review is to analyze the main and most recent imaging techniques in the endoscopic field, paying particular attention to their real applicability to clinical practice, analyzing the main advantages and major limitations for each technique.

**Background:** In recent years, several innovations have been introduced in the field of endoscopy but, even if they seem to bring significant advantages, it is necessary to systematically analyze the field of application and the real clinical advantage. The aim of this review is to analyze literature in order to define the real usefulness of each technique.

**Methods:** A review of the literature was conducted on MEDLINE, PubMed, Cochrane Library. Studies were included in English language. Randomized controlled trial, meta analysis, review in the endoscopic field were included. A narrative analysis with the evaluation of advantages and disadvantages of each technique was conducted.

**Conclusions:** The techniques here analyzed offer several advantages and allow an improvement in the management of the endoscopic patient. However, each technique requires specific experience and a specific field of application. For each method, there is the need to define through further studies the real field of application and to ensure a better performance in clinical practice.

**Keywords:** Endoscopic imaging; artificial intelligence (AI); confocal endomicroscopy (CE); endoscopy

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## Introduction

### Background

Since the introduction of the first Olympus gastroscope in 1950, which allowed to directly obtain images of the stomach, a real revolution in endoscopic imaging techniques has been reached, either through the correction and qualitative improvement of the images (for example through the introduction of high definition), or through the introduction of new techniques and complementary tools that allowed to considerably raise the diagnostic level of

endoscopy.

Among these elements, the main innovations introduced over the past years that allowed a first significant diagnostic improvement, were: the chromoendoscopy, consisting in the use of dyes able to highlight pathological changes in the mucosa, and digital chromoendoscopy, such as narrow band imaging (NBI), flexible spectral imaging color enhancement (FICE) and iScan, consisting in an electronic image allowing the evaluation of superficial mucosal lesions. More recently, in order to further improve the diagnostic accuracy of the endoscopic examination and reduce the possibility

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of human error, artificial intelligence (AI) has also been introduced in endoscopy, which would guarantee the possibility of identifying and processing small lesions that could escape to the human eye. In addition, a further step forward from the diagnostic point of view is represented by confocal laser endomicroscopy (CLE), a method that, through a magnification of the cellular structures under examination, would allow a histological diagnosis *in vivo*, which could improve the identification of pathological areas.

### Objectives

The goal of our research was to identify the most recent and significant studies and meta-analyses regarding the main endoscopic imaging techniques. Subsequently, we analyzed the papers by paying attention to the field of applicability of each method, evaluating advantages and disadvantages in real clinical practice. According to us, these evaluations can be advantageous in order to implement these methods in clinical practice, obtaining an improvement in the diagnostic-therapeutic path and in the cost/benefit ratio.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/dmr-21-57>).

### Methods

We performed a systematic review of literature searching in MEDLINE, PubMed, Cochrane Library. Studies were included in English language. Randomized controlled trial, meta analysis, review in the endoscopic field from 2001 to 2021 were included.

### Discussion

#### Chromoendoscopy

Chromoendoscopy involves the use of different types of chemical dyes which, directly applied on the mucosa during the endoscopic examination through the use of a probe, allow to distinguish between normal and altered mucosa (1). This method is mainly applied in the evaluation of suspicious areas in Barrett's esophagus, in the identification of dysplastic lesions in inflammatory bowel diseases (IBD), in the detection of early gastric cancer (EGC).

#### Acetic acid (AA) in the Barrett

In the evaluation of Barrett's esophagus, the distinction between non-dysplastic areas from high-grade dysplasia (HGD)/EGC is essential. In this sense, the use of AA in Barrett's esophagus conceived by Guelrud and colleagues in 2001 (2), significantly improves the diagnostic accuracy. In fact, the application of AA on the esophageal mucosa causes a so-called "aceto whitening reaction" (3) which is lost rapidly (23–53 s) by HGD/EGC lesions, compared to non-dysplastic lesions (4). Furthermore, as demonstrated by Coletta *et al.* (5), staining with AA chromoendoscopy has a high diagnostic accuracy in the detection of HGD/EGC, regardless of the use of magnification, with a sensitivity and a specificity of 92% and 96% respectively. The main advantage of this technique is in the low cost of the material, in the universal application to any type of endoscope, and could be cost-effectiveness, drastically reducing the number of biopsies necessary for the identification of suspicious areas as demonstrated by the Portsmouth group (6). On the other hand, preventive training is required and other large-scale studies are needed to replace the use of random biopsies in the four quadrants.

#### AA and indigo carmine in gastric cancer

A further area of challenge is represented by EGC, which has a significant incidence increase, especially related to the implementation of screening programs in countries with a higher incidence such as Korea and Japan. EGC is defined as a tumor confined to the mucosa or submucosa and, for this reason, from diagnosis to treatment, is becoming more and more of exclusively endoscopic interest.

From a diagnostic point of view, several studies demonstrated a clear superiority of detection of endoscopic examinations carried out with chromoendoscopy using different dyes such as indigo carmine, methylene blue or hematoxylin (7-9). Furthermore, a recent meta-analysis by Zhao *et al.* (10) comprising 699 patients for a total of 902 lesions, demonstrated that chromoendoscopy has a diagnostic sensitivity and specificity of 90% and 82% respectively, significantly higher than traditional white light.

Moreover, considering that endoscopic resection of these tumors is the first choice, in particular using submucosal endoscopic dissection (ESD), it is clear that a precise assessment and definition of the lesion is strictly necessary.

This element is essential for any lesion to be resected endoscopically but represents a key problem in EGC, since these are frequently flat lesions with poorly defined margins.

In this sense, chromoendoscopy using a solution of carmine indigo added to AA allows to increase the diagnostic performance in order to ensure an effective treatment. The study by Sakai *et al.* (11) of 2008 clearly demonstrates the superiority of the performance rate with this solution (94.3%) both with respect to traditional light (17%), and to coloring with only indigo carmine (52.8%) or only AA (41.5%).

This superiority was also confirmed by subsequent studies. In fact, a paper by Lee *et al.* (12) in which 141 patients were included, highlighted that with this mixed staining, the ability to distinguish the margins of the lesion was obtained in 84.1% compared to 66.9% of conventional endoscopy.

In conclusion, the solution of indigo carmine and AA represents an easy, fast, inexpensive method in the evaluation of EGC and is very useful, if not necessary, in evaluating the margins in order to obtain a complete endoscopic resection.

### **Chromoendoscopy in IBD**

Another relevant application of chromoendoscopy consist in the identification of dysplastic lesions of the colon, particularly in patients with IBD. In fact, in these patients, the dysplastic lesions are often flat and difficult to identify. In this sense the international guidelines recommend an extensive random biopsy sampling with biopsies over the four quadrants every 10 cm (13) although poor evidence support this indication (14). However, the improvement of endoscopic imaging with high resolution and with the use of chromoendoscopy has implemented the possibility of identifying precancerous or neoplastic lesions, particularly in these patients. Thus, during a colonoscopy with chromoendoscopy, a dye such as methylene blue or carmine indigo is applied along the colonic profile with a spray catheter or in the water jet channel in order to increase the contrast. For this reason, the use of chromoendoscopy in the surveillance of colon cancer in IBD patients is highlighted by the consensus Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC-ICS) (15). Despite these indications, the method has some limitations. In fact, a

recent meta-analysis (16) has shown that chromoendoscopy in IBD patients offers only limited advantages in the detection of suspicious lesions. Furthermore, it also appears to be time consuming and requires excellent intestinal preparation and disease in remission or in mild activity. Despite these limitations, it is still a valid tool especially in selected patients.

### **Virtual chromoendoscopy**

Recently, in addition to the traditional chromoendoscopy, virtual coloration has been introduced in endoscopy. Through dedicated endoscopes, the mucosa is analyzed with specific wavelengths of light, capable of magnifying the image and highlighting specific characteristics of the mucosa. The main types are NBI, introduced by Olympus, FICE, introduced by Fujinon, and iScan introduced by Pentax.

### **NBI**

NBI is a virtual staining technique based on the separation of light through the use of filters, allowing only blue light to penetrate deep into the mucosa to highlight the superficial vascularization of the lesions making them more evident (17,18). In this area, the main focus is in the assessment of colic lesions with the aim of identifying the histological characteristics of the polyp during the examination. In this sense, several studies have shown that the use of NBI allows an improvement in the adenoma detection rate (19,20) in particular compared to white light, although this improvement does not seem to be superior to chromoendoscopy, as demonstrated by a previous meta analysis by van den Broek *et al.* (21). However, it should be emphasized that the use of NBI is quicker and more immediate than traditional chromoendoscopy as it does not require the introduction of specific probes or dyes.

In order to standardize this method, various classifications have been proposed based on the characteristics of the lesion. The main classification is the NBI international classification endoscopic (NICE) (22) which classifies polyps into 3 different types, type 1 hyperplastic, type 2 adenomatous, type 3 neoplastic (*Table 1*). Therefore, the introduction of this classification would reduce the need for biopsies and unnecessary resection of polyps, with the reduction of complication rates.

### **FICE**

FICE is a computerized virtual chromoendoscopy based on

**Table 1** NICE classification with macroscopic characteristics

Parameter	Type 1	Type 2	Type 3
Vessels	No vessels or small vessels	Brown vessels in white background	Disrupting or missing vessels
Colour	Overlapping or lighter than the background	Darker than the surrounding tissue	Brown or very dark compared to the surrounding area, sometimes with white areas
Surface pattern	Small dark or white spots or uniform absence	Oval, tubular or whitish branching structures surrounded by vessels	Totally amorphous or absent structure
Histology	Hyperplastic or serrated	Adenoma	Neoplasia

NICE, narrow band imaging international classification endoscopic.

the digital reconstruction of the image, making the mucosa appear as if it was illuminated at different wavelengths that can be specifically selected. This allows you to rework the images even after the examination, which is the great advantage of this type of coloring.

The FICE has also been subjected to several studies in order to evaluate the advantages that it brings during endoscopic examinations. Thus, in the evaluation of Barrett's esophagus, a study by Camus *et al.* (23) has shown that FICE in association with chromoendoscopy with AA, drastically improves the study of this condition. On the other hand, in the evaluation of colic lesions, a large randomized controlled study has shown that with FICE the ADR is not higher than with traditional white light (24). Furthermore, a comparison study was also conducted between NBI and FICE and it demonstrated a good correlation of both methods with histology, while there was no substantial difference between FICE and NBI (25).

### Endocytoscopy

One of the essential points for diagnostic improvement in the field of endoscopy is the magnification of the image which, in recent years, has seen a marked increase in techniques and methods. In this context, in the last twenty years a technique has seen a growing evolution, endocytoscopy. The endocystoscope system consists of a flexible microscope that allows an evaluation with magnification of lesions or areas of the gastrointestinal tract aimed, also through the use of dyes during the endoscopic procedure, to define histological profiles (26).

Introduced by Olympus in 2003 with a probe that was introduced within the operating channel, it had some use limitations related to robustness. Subsequently, evolutions

of this method were developed up to the fourth generation of endocystoscope integrated into the instrument and with a magnification allowed up to  $\times 500$ .

In 2011 a first classification of colic lesions was proposed by Kudo (27). In his series comprising 206 patients, the colic lesions studied by endocytoscopy were classified into different groups: EC1a for normal mucosa, EC1b for hyperplastic lesions, EC2 for dysplastic lesions and EC3 for invasive lesions.

Starting from these bases, several studies have been conducted in order to define the role of this method in the evaluation of lesions of the upper gastro esophageal tract. In the esophagus, a study by Eleftheriadis *et al.* (28) in which the results of endocytoscopy were compared with the results of histology, demonstrated a good utility and reliability of the method. In addition, another study by Tomizawa *et al.* (29) demonstrated 90% diagnostic accuracy for experienced operators with good inter observer agreement (85%).

Obviously, the endocytoscopy finds an excellent application also in the study of lower digestive tract. Starting from the Kudo classification (27), several studies have been conducted in order to define the degree of diagnostic accuracy. Overall, it has been estimated in different papers, that the diagnostic accuracy of this method in discerning between neoplastic and non-neoplastic diminutive lesions (<5 mm) is between 93.3% and 96.8% (30,31). In addition, another relevant point is the possibility of assessing the degree of infiltration. Several studies have shown that compared to assessment based on the pit pattern, endocytoscopy has a better performance (32,33).

Overall, endocytoscopy, in particular the latest generations of instruments, seem to guarantee a better diagnostic performance allowing an *in vivo* histology. However, this method also has some limitations. The

first is linked to the limited availability of endocytoscopes that limit the diffusion of the method. Secondly, the lack of standardization in the classification of lesions leads to a lack of certain criteria. Furthermore, the impossibility of evaluating beyond the mucous layer and, therefore, of evaluating the depth of the lesion, limits the diagnostic power of the method. Further studies are therefore needed to establish the real clinical utility and applicability.

### **Confocal endomicroscopy (CE)**

A potentially relevant method in endoscopy is represented by CLE. In this field there are two possibilities: the endoscope-based confocal laser endomicroscopy (eCLE) introduced by Pentax, and the confocal laser endomicroscopy using a probe (pCLE) introduced by Cellvizio. In this technique, the microscope uses a specific wavelength of laser light which, hitting the tissue, allows a two-dimensional reconstruction of the images. For this technique, it is necessary to use contrast agents such as fluorescein or cresyl violet, which can be used both systemically and topically. Once applied, it is necessary to place the probe in direct contact with the surface to be examined with sufficient stability in order to allow *in vivo* evaluation.

The goal is to allow a greater accuracy in the evaluation and identification of suspicious lesions in the gastrointestinal tract, with a considerably higher precision than standard methods (white light, chromium virtual endoscopy), as it would also convey, *in vivo* and during the endoscopic examination, a 1,000-fold magnification of the cellular structures, allowing the realization of an *in vivo* histology. For this reason, one of its major uses is in the field of IBD both in the assessment of the degree of inflammation, in particular by considering the distortion of the crypts and in the presence of fluorescein between cell junctions (34), and in the evaluation of the response to therapy (35). In addition, it could be useful in the evaluation of suspected lesions or areas at risk of neoplastic degeneration. In fact, Kiesslich *et al.* (36) have shown that CE is able to increase the early detection of neoplastic lesions up to 4.75 times the normal, reducing the number of biopsies and with a time comparable to a standard endoscopic examination.

Furthermore, other applications are related to an early diagnosis of precancerous and cancerous lesions. Again, particular interest is in the evaluation of dysplasia in Barrett's esophagus. In this context, di Pietro *et al.* (37) have developed diagnostic criteria for the evaluation of dysplasia

in the Barret.

On the one hand, CE is a method of great interest both for the various applications and for the possibility of obtaining a histology *in vivo* which reduces the need for biopsies and which can guide diagnostic-therapeutic choices more quickly. On the other hand, the main limitation is in the learning curve of the method and the limited availability of scores and diagnostic criteria. Further studies are needed in order to define diagnostic criteria and precise the field of application of this technique.

### **AI**

One of the most recent topics in the field of technological innovations in endoscopy is represented by AI, which consists of a machine capable of learning and improving its performance without the need of programming. This system has already been applied in the medical field in radiology, ophthalmology and dermatology, but only recently has it also been introduced in endoscopy. After initial difficulties, the introduction of data-driven deep learning (DL) made it possible to make the process extremely efficient (38) through the learning and classification of an enormous number of images and the creation of algorithms, including the convolution neural network (CNN), the most widespread in the medical field.

In endoscopy, the starting point was assistance during colonoscopy in order to (I) improve the adenoma detection rate, defined as computer-aided detection (CADe), and (II) facilitate the interpretation of the lesions, allowing the differentiation between benign polyp and precancerous forms, defined as computer aided diagnosis (CADx).

### **CADe**

The adenoma detection rate represents the true element of prevention in colon cancer. In this sense, the increase of this index allows to dramatically reduce the incidence of neoplasms and that is why AI could represent a turning point. A first study was conducted by Wang *et al.* (39) on the automatic detection of colonic polyps by the DL, during colonoscopy. In this study, it has been shown that on a total of 1,058 patients AI has allowed to significantly increase the ADR from 20.3% to 29.1% ( $P < 0.001$ ) and the average number of adenomas per patient from 0.31 to 0.53 ( $P < 0.001$ ) with a significant increase in the finding of diminutive lesions, which are more easily not to be detected by the endoscopist. In addition, a recent meta analysis conducted by Hassan *et al.* (40), which included 5 randomized

controlled trials, showed that ADR is statistically higher in CADe than in controls (36.6% *vs.* 25.2%) and the number of polyps found by colonoscopy is higher with AI. Overall, these data show that, although experience is still required in this area, AI can lead to a significant improvement in ADR and, therefore, in the prevention of cancer.

### CADx

The main purpose of CADx is to predict the histology of lesions found during colonoscopy. The goal is to optimize the procedures during the examination, in order to reduce the number of biopsies, unnecessary endoscopic resections, for example those of hyperplastic polyps, reducing the costs related to devices and possible periprocedural complications. In this sense, a first pilot study was conducted in 2010 by Tischendorf *et al.* (41) which based its evaluation on the polyp vascularization assessed with NBI and compared the sensitivity and specificity in the classification of polyps between experienced endoscopists and computer. In this study, the AI proved to be reliable, but the evaluation of the experts remained superior with a sensitivity and specificity of 93.8% and 85.7% *vs.* 90% and 70%, respectively. From this first point, other studies and algorithms have been developed with a clear improvement in performance. In particular, a study conducted by van der Zander *et al.* (42) based on the use of a database of 2,449 polyps, showed that the diagnostic accuracy using high definition with white light was 88.3% and 86.7% using NBI, but the combination of the two methods (multimodal imaging) achieved an accuracy of 95%, statistically superior to that of experienced endoscopists. Other studies and any specific algorithms will have to be evaluated with specific studies.

In this sense, AI represents a potentially revolutionary resource in the field of endoscopy but still has many limitations related to actual application in clinical practice. In the review by Ahmad *et al.* (43) it is emphasized that most of the studies currently available are limited and are retrospective studies that cannot alone represent elements of validation of the method. In addition, it is still necessary to clarify some elements such as the real reliability of the system, the legal aspect and the reimbursement of the method. This review suggests how the integration of AI with patient-specific information, where available, can represent a further useful improvement element.

In conclusion, AI promises to be an advantageous tool to improve the quality of endoscopy but necessarily requires important collaborative efforts between clinicians, engineers and programmers in order to perfect the method.

Subsequently, robust clinical trials are needed to confirm the reliability and efficiency of the method and to find the best way to implement it in clinical practice.

### Conclusions

In conclusion, the introduction of new endoscopic imaging techniques has allowed to improve the general quality of endoscopic examinations. However, each of them requires a learning curve and experience that allows you to use each single technique in the field and in the most appropriate way. Furthermore, studies are still needed to define scores and standards that have a real and easy applicability to the clinic.

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