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**Kyoto classification of gastritis, virtual chromoendoscopy and artificial intelligence: Where are we going? What do we need?**

Panarese A *et al*. Classification of gastritis

Alba Panarese, Yutaka Saito, Rocco Maurizio Zagari

**Alba Panarese,** Division of Gastroenterology and Digestive Endoscopy, Department of Medical Sciences, Central Hospital - Azienda Ospedaliera, Taranto 74123, Italy

**Yutaka Saito,** Division of Endoscopy, National Cancer Center Hospital, Tokyo 104-0045, Japan

**Rocco Maurizio Zagari,** Gastroenterology Unit and Department of Surgical and Medical Sciences, IRCCS Azienda Ospedaliero-Universitaria and University of Bologna, Bologna 40121, Italy

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**Corresponding author: Alba Panarese, MD, Chief Physician, Director,** Division of Gastroenterology and Digestive Endoscopy, Department of Medical Sciences, Central Hospital - Azienda Ospedaliera, Francesco Bruno Street, 1, Taranto 74123, Italy. albapanarese@libero.it

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**Abstract**
Chronic gastritis (CG) is a widespread and frequent disease, maily caused by *Helicobacter pylori* infection, that is associated with an increased risk of gastric cancer. Virtual chromoendoscopy improves endoscopic diagnostic efficacy, which is essential to establish the most appropriate therapy and to enable cancer prevention. Artificial intelligence provides algorithms for the diagnosis of gastritis, and, in particular, early gastric cancer, but it is not yet used in practice. Thus, technological innovation, through image resolution and processing, optimizes the diagnosis and management of CG and gastric cancer. The endoscopic Kyoto classification of gastritis improves the diagnosis and management of this disease, but through the analysis of the most recent literature new algorithms can be proposed.

**Key Words:** Early gastric cancer; Artificial intelligence; *Helicobacter pylori*; Dysplasia; Image enhanced endoscopy; Kyoto classification of gastritis

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**Core Tip:** Advances in virtual chromoendoscopy have improved the knowledge and management of chronic gastritis and led to the Kyoto classification. Artificial intelligence promotes the progression in the management of the gastric cancer and the diffusion of innovation, allowing new diagnostic algorithms that include both active inflammation and dysplasia as evolutionary steps towards cancer.

**INTRODUCTION**

Chronic gastritis (CG) is a widespread and frequent disease, often undiagnosed even after a gastroscopy. Chronic gastritis is relevant to the symptoms it expresses, for the absorption defects it can entail, but, above all, for the oncological risk to which it is associated[1]. The correct diagnosis improves the management of the disease and, on the endoscopic side, the identification of dysplasia and early gastric cancer is fundamental, possible due to advances in endoscopic technology, which allows the observation of the gastric mucosa in detail[2]. The appropriate classification of CG, defining the etiology, severity, extention, and in particular the oncological risk, allows the correct management of the disease and contributes to the results of artificial intelligence, capable of developing algorithms for the diagnosis of CG and gastric cancer[3-6].

Objectively, considering that the gastric cancer is still a major cancer, the diagnosis of dysplasia is a relevant outcome[3,7,8] and the endoscopic surveillance, important for detecting dyplasia and gastric cancer, is efficient in the high-risk population[9,10]. Early stage gastric cancer can be cured *via* endoscopic submucosal dissection, that is curative and less invasive than surgery if carried out according to the guidelines[11-13].

*Helicobacter pylori* (*H. pylori*) infection is the main cause of CG and gastric cancer [14]. *H. pylori* is a type I carcinogen for gastric cancer [15]. However, the risk of gastric cancer in *H. pylori* positive subjects is related to the development of precancerous conditions, i.e. mucosal atrophy (MA) and intestinal metaplasia (IM)[14,16-18]. Indeed, gastric cancer morbidity and mortality are reducing by *H. pylori* eradication therapy [19]. Therefore, the accurate assessment of *H. pylori* infection status is important[20-22]. The $^{13}C$-urea breath test, stool antigen test and sierology are non-invasive tests for the diagnosis of *H. pylori* infection[5,22].

The Kyoto classification of gastritis, advocated in 2013, in Kyoto, during the 85th Congress of the Japan Gastroenterological Endoscopy Society, was developed with the aim of endoscopically diagnosing *H. pylori* infection and assessing risk factors for gastric cancer[23].

This review is an up-to-date on the Kyoto classification of gastritis[3,23] and highlights advances and future in endoscopic diagnosis of gastritis and gastric cancer to help improving endoscopic practice.

## THE KYOTO CLASSIFICATION OF GASTRITIS

The Kyoto classification of gastritis accurately considers the endoscopic characteristics of gastritis associated with *H. pylori* infection and identifies gastric cancer risk factors[23].

In the Kyoto classification of gastritis, there are 19 characterized endoscopic findings that are related with presence/absence of *H. pylori* infection, gastritis and the risk of gastric cancer (Table 1). Among them, MA, IM, enlarged folds, nodularity and diffuse redness are accounted for in the Kyoto classification score, which is the sum of scores of them. The Kyoto score ranges from 0 to 8 (Table 2) and a high score reflects a higher risk of current *H. pylori* infection and gastric cancer[23].

The endoscopic MA (Figure 1A) consists of discolored/pale mucosa with a visible capillary network, and is classified according to the Kimura and Takemoto classification[24], widely used to diagnose atrophic border using white light imaging (WLI). In Japan, this classification correlates with histological findings and serum pepsinogen level observed in case of MA[24,25], while, in Western countries, WLI cannot correctly diagnose MA and IM according to guidelines, which recommended gastric biopsies for the confirmation of MA, as for IM[26].

The endoscopic IM (Figure 1B) looks as an irregular surface with slightly elevated/flat/depressed grayish-white plaques surrounded by mixed patchy pink and pale areas of the mucosa. Useful indicators for the endoscopic diagnosis of IM are villous patterns, whitish colors, and rough surfaces, distinctly visible with virtual chromoendoscopy (Figure 2). WLI presents low sensitivity for diagnosis of IM compared to that of the pathological diagnosis[16,25].

The enlarged folds (Figure 1C) are folds of the body with a width ≥ 5 mm, because of increased mucosal thickness due to foveolar hyperplasia and massive infiltration of inflammatory cells. Insufflation does not flatten them or does so partially. The thickness of the folds normalizes after the eradication of *H. pylori*[10,23].

Nodularity (Figure 1D), *i.e.* nodular gastritis, is localized mainly in the antrum and consists of a nodular or micronodular diffuse pattern of the mucosa, similar to "goosebumps". Nodular antral gastritis pathologically consists of prominent lymphoid follicles with infiltration of mononuclear cells. It can be observed more frequently in the stomach of children than in that of adults, suggesting to be a characteristic of the early stage of *H. pylori* infection[27-29].

Diffuse redness (Figure 1E) is the uniform redness of the non-atrophic fundic mucosa, expression of the congestion and dilation of the subepithelial capillary network by inflammation with the infiltration of neutrophils and mononuclear cells[30].

Regular arrangement of collecting venules (Figure 1F), in the corpus, from a distance, appears as numerous dots and, up close, as a regular pattern of starfish-like shapes.

## THE EFFECTIVENESS OF THE KYOTO CLASSIFICATION OF GASTRITIS

The effectiveness of the Kyoto classification of gastritis is proven by testing scores in patients with CG, gastritis associated with *H. pylori*, and gastric cancer.

## DIAGNOSIS OF *H. PYLORI*-RELATED CHRONIC GASTRITIS

The Kyoto classification proposes the endoscopic diagnosis of *H. pylori* infection status, although the diagnostic confirmation comes from other investigations[5,17]. Endoscopic diagnosis of *H. pylori* infection by WLI has low sensitivity (18%-75%) and poor inter-observer agreement[31,32], while magnified image-enhanced endoscopy (M-IEE) is more accurate[9-10,26].

Regarding active *H. pylori* infection reletad-gastritis, enlarged folds, nodularity and diffuse redness have low sensitivity, but a good specificity, in particular for nodularity (sensitivity: 6.4%-32.1%, specificity: 95.8%-98.8%). On the other hands, regular arrangement of collecting venules have high sensitivity for non-infection (86.7%-100%). Furthermore, for the diagnosis of past *H. pylori* infection, endoscopic MA has lower specificity (75.5%) compared to IM and map like redness (92.6% and 98.0%, respectively)[33].

Regarding total Kyoto classification score and serum *H. pylori* antibody titer, Kyoto scores increase in line with the *H. pylori* antibody titer[34,35].

A Kyoto score of 0, 1, and ≥ 2 and no history of *H. pylori* eradication therapy, corresponds to *H. pylori* infection rates of 1.5%, 45%, and 82%. However, an active *H. pylori* infection is not always present in case of high Kyoto scores, due to a spontaneous negative conversion, IM, or an unintentional eradication, after the treatment of other infectious diseases with antibiotics[35,36].

## ASSESSMENT OF THE RISK OF GASTRIC CANCER

It has been reported a good agreement between endoscopic findings for MA and IM and histopathological diagnosis[36]. Endoscopic determination of IM in the corpus is useful because when endoscopic IM is present in the corpus (*i.e.* the IM 2 score of the Kyoto classification), the pathological IM is significantly associated with a higher risk of gastric cancer[38]. Furthurmore, corpus-predominant activity, i.e. the presence of neutrophil activity, has a higher risk of gastric cancer than antral predominant activity[38]. Severe endoscopic MA, enlarged folds, and nodularity correspond to an higher neutrophil activity in the corpus than that in the antrum[37].

The topographic distribution of neutrophil activity and IM is strongly associated with gastric cancer risk and corresponds to the separate assessment of pathological gastritis in the corpus and antrum [38].

Regarding the gastric cancer assessed by the Kyoto classification of gastritis, its incidence increases, as %/year, for mild (0.04-0.10), moderate (0.12-0.34), and severe (0.31-1.60) atrophy[38-40]. In detail, over a period of 10 years, the incidence is extremely high (16.0% of patients with severe atrophy)[16] and increases according to the extent of the MA. The prevalence of O-II/O-III-type atrophy according to the Kimura-Takemoto classification is significantly higher in patients with gastric cancer than in subjects with gastritis alone (45.1% vs 12.7%, $P < 0.001$)[10,39]; and Kyoto gastritis scores of MA and IM are significantly higher in the *H. pylori* -positive cancer group than in subjects with gastritis alone ($P < 0.001$). Furthermore, endoscopic IM is associated with intestinal-type early gastric cancer with an OR of 5.0; enlarged folds and nodularity are associated with diffuse-type gastric cancer with an OR of 5.0 and 13.9, respectively[10].

A cross-sectional study suggests that a Kyoto classification score of ≥ 4 might indicate gastric cancer risk considering that the Kyoto classification score is 4.8 and 3.8, respectively, for patients with and without gastric cancer[10].

## VIRTUAL CHROMOENDOSCOPY FOR THE DIAGNOSIS OF CHRONIC GASTRITIS AND GASTRIC CANCER

Virtual chromoendoscopy is necessary for a correct evaluation of CG because remarkably improves the accuracy in the diagnosis of premalignant lesions and early gastric cancer, increasing the visibility of endoscopic findings[26]. Image-enhanced endoscopy (narrow-band imaging, NBI, linked color imaging, LCI, blue laser imaging, BLI, texture and color enhancement imaging, TXI, and autofluorescence imaging) achieves significantly better sensitivity and specificity than WLI, due to the examination of the glandular epithelium by observing the microvascular architecture and structure of the microsurface[31,32,41,42]. However, M-IEE requires skills and experience[43].

Narrow band imaging, through narrower band lights by blue and green filters, enhances visualization of the vascular, more than surface, structure of the mucosa[44]. Magnified narrow band imaging can accurately diagnose inflammation and premalignant conditions with a sensitivity higher that that of WLI[31,41,42]. Yellowish-white nodules are predictive marker of nodular gastritis because have a high specificity for the histological finding of lymphoid follicles in *H. pylori* -positive stomach [42]. The presence of a fine blue-white line on the crests of the epithelial surface, light blue crest, and white opaque substance, an accumulation of lipid micro-droplets in the superficial area of certain IM, are highly accurate signs of IM[31,41]. Correspondence between histology and magnified narrow band imaging has been verified regarding the diagnosis of IM and MA[31,41].

Autofluorescence imaging detects natural fluorescence of some components of gastric mucosa in real time during endoscopy to differentiate between non-atrophic mucosa, purple, and atrophic mucosa infected with *H. pylori*, green[45]. However, current endoscopic systems do not have the autofluorescence imaging function. Otherwise, texture and color enhancement imaging clearly define subtle tissue differences due to the enhancement of three image factors in WLI (texture, brightness, and color). It is available on the new generation Olympus instruments[46].

Blue laser imaging-bright and linked color imaging use narrow-band short wavelength light because separately correct blue, green and red color information. Blue laser imaging, as in narrow band imaging, produces red color high-intensity contrast enhanced images, through blue and green color information, allowing superior visualization of microvascular and microsurface patterns. In blue laser imaging-bright the spotty pattern is correlated with the active *H. pylori* infection, the cracked pattern corresponds to the post-inflammatory change after the eradication of *H. pylori* and the mottled pattern to IM[46]. Linked color imaging uses the information of all three colors and returns images with color enhancement in its own color range (*e.g.*, red is changed to vivid red and white to clear white) by unique image processing. Regardless of *H. pylori* infection status, linked color imaging, compared to WLI, increases the color difference around the atrophic border. Linked color imaging identifies diffuse redness of the fundus as a crimson red color; and, compared to WLI, offers a significantly higher overall diagnostic accuracy in patients with *H. pylori*-positive stomach and those with *H. pylori*-negative stomach after eradication. On the contrary, regarding the presence of regular arrangement of collecting venules or diffuse redness, WLI, linked color imaging, and magnifying endoscopy with WLI have similar diagnostic accuracy for *H. pylori* infection. Linked color imaging identifies IM as a lavender color and the diagnostic accuracy is significantly higher than in WLI. Moreover, it increases the visibility of diffuse redness, spotty redness, map like redness, patchy redness, red streaks, and atrophic border. Bright-Blue laser imaging- improves IM visibility[48].

Magnified-IEE allows the correct endoscopic diagnosis of gastritis with the application of the Kyoto classification of gastritis, and guarantees accuracy and reproducibility of endoscopic diagnosis for premalignant lesions related to *H. pylori* infection throughout the stomach during active infection and after the eradication of *H. pylori*[49].

## ARTIFICIAL INTELLIGENCE FOR THE DIAGNOSIS OF CHRONIC GASTRITIS AND GASTRIC CANCER

Artificial intelligence, based on deep learning, which has made considerable progress in various fields through the convolutional neural network (CNN), a method for image recognition, can be trained with endoscopic images and could detect gastric cancer accurately[4,50]. Artificial intelligence autonomously extracts and learns discriminative features of the images and analyzes complex features of them, including shapes, colors, and textures. So far, several artificial intelligence-assisted CNN Computer-Aided Diagnosis systems have been built, whose diagnostic accuracy in detecting CG and gastric cancer is based on WLI and/or IEE[4,51-53], thus allowing a better performance of endoscopists. However, since their introduction in this field is recent, the results of most studies need to be further validated, considering all the aspects of endoscopy and formulating increasingly advanced algorithms.

Prospective studies suggest that the deep learning based real-time video monitoring diagnostic model works better than endoscopists in the diagnosis of CG and gastric cancer[6,52] and that Computer-Aided Diagnosis systems based on deep learning algorithm have a significantly higher accuracy for IEE than for WLI[54]. Computer-Aided Diagnosis has been studied with Kyoto classification of gastritis for endoscopic diagnosis of *H. pylori* infection, demonstrating an accuracy similar to that of experienced endoscopists, superior with IEE rather than using WLI. Real-time analyses is validating in prospective studies the accuracy of Computer-Aided Diagnosis with IEE, using Kyoto classification of gastritis for diagnosing *H. pylori* infection and evaluating the gastric cancer risk [55].

**FUTURE PERSPECTIVES IN ASSESSMENT OF CHRONIC GASTRITIS**

Technological developments in IEE allow high diagnostic performance to identify CG and determine the risk of gastric cancer according to the Kyoto classification of gastritis[33]. Magnified narrow band imaging identifies MA and IM because of its detailed examination of the gastric mucosal pattern light blue crest and white opaque substance[26,31]. At a distant view, non-magnified narrow band imaging, blue laser imaging-bright and autofluorescence imaging are useful for evaluating MA and IM, and linked color imaging for diagnosing MA, IM, diffuse redness and regular arrangement of collecting venules, compared with WLI. Linked colour imaging allows the highest visibility among findings of the Kyoto classification of gastritis and early gastric cancer after *H. pylori* eradication. Blue laser imaging has the highest visibility of microvascular pattern, microsurface pattern, and demarcation line in magnifying observation[41,42,47,48]. Matsumura *et al*[49] suggest that the best methods for detecting and diagnosing early gastric cancer after *H. pylori* eradication are linked color imaging observation of the stomach and magnifying blue laser imaging, respectively, [33].

Furthermore, in the evaluation of gastric cancer risk, the total score of the grading system is useful in patients with active *H. pylori* gastritis[10,39], but after *H. pylori* eradication may not be accurate because of the disappearance of diffuse redness, enlarged folds and nodularity. Moreover, the absence of regular arrangement of collecting venules is identified as independent risk of gastric cancer after *H. pylori* eradication[56,57]. Therefore, studies with IEE, applying the Kyoto classification of gastritis, require prospective confirmation and a new grading system, which includes the findings of MA, IM and regular arrangement of collecting venules to assess the risk of gastric cancer in patients with past *H. pylori* infection.

Secondly, GC is a disease with two important etiologies, *H. pylori* infection and autoimmunity, worthy of different treatments and surveillance to reduce the risk of gastric cancer, which could remain a frequent cancer precisely because the prevalence of *H. pylori* infection will decrease, but the incidence of autoimmune gastritis will increase[21,58]. Definitive endoscopic diagnostic criteria should be established for autoimmune gastritis, in addition to the dosage of antibodies, and should be considered endoscopic findings[3,59]. A new endoscopic classification that considers *H. pylori* gastritis as well as autoimmune gastritis is desirable. Regarding *H. pylori* related gastritis, the endoscopic diagnosis of *H. pylori* infection must be confirmed by an additional test for *H. pylori* including histology or 13C-urea breath test. Endoscopic diagnosis is not sufficient to prescribe antibiotic therapy, even if, due to recent advances in IEE, diagnostic accuracy is improved and the Kyoto classification of gastritis unifies endoscopic diagnostic criteria for gastritis allowing the association between gastritis and *H. pylori* infection. Eradication therapy of *H. pylori* is prescribed if positivity is confirmed by 13C-urea breath test, histological examination or fecal test[21]. In conclusion, currently, it is not possible to determine a conclusive diagnosis of active *H. pylori* infection endoscopically only.

Thirdly, MA, enlarged folds, nodularity, diffuse redness and regular arrangement of collecting venules have been considered to assess correlation between endoscopic findings and histopathology[33], with the limit that only the combinations of different endoscopic findings can improve diagnostic accuracy because no single endoscopic feature is highly specific for histological MA and inflammation[23]. However, endoscopic MA and IM are associated with pathological atrophy and IM, respectively, according to several studies[37-59]; and the Kyoto classification of gastritis score correlates with the activity and distribution of neutrophil, which are related to the risk of cancer[60]. It is necessary to point out, however, that studies on the consistency between the Kyoto classification of gastritis and histology based on the updated Sydney system are few.

Fourthly, endoscopy-based Kyoto classification of gastritis scare, that predicts the risk of gastric cancer, changes after *H. pylori* eradication. Toyoshima *et al*, in a retrospective study, conclude that the Kyoto classification score decreases after *H. pylori* eradication for enlarged folds, nodularity and diffuse redness[61]. Probably, we should calculate the score after eradication of *H. pylori* infection to better define the cancer risk and the need for surveillance. As for other preneoplastic conditions of the digestive tract, *i.e.* Barrett's esophagus, it is necessary to estimate the score when the inflammation is not active. High-resolution WLI, in association with narrow band imaging, increase low grade dyplasia detection on visible lesions after regression of active *H. pylori*-induced chronic gastritis. An extensive gastric mapping is required in patients with an overlap between autoimmune atrophic gastritis and *H. pylori*-induced gastritis [40,49,61,62].

In a future consensus setting, a new algorithm should be published[3]. Considering that *H. pylori* is oncogenous, we should screen for *H. pylori* infection, treat positives, and then perform gastroscopy when the infection is no longer active and the possibility of detecting dysplasia is greater. Indeed, dysplasia is the real condition that increases the risk for gastric cancer[63,64]. Current technologies make it possible to detect dysplasia[64], which must be included in the final score as a new finding. Of course, we must perform high quality gastroscopy and, currently, biopsies must be carried out with M-IEE, for an accurate histological assessment of gastritis[26]. The accuracy of M-IEE in trained hands further increases the yield of targeted biopsies, necessary for a correct risk stratification with OLGA – OLGIM histological staging systems (Operative Link for Gastritis Assessment, Operative Link for Gastric Intestinal Metaplasia Assessment)[65]. Patients in OLGA and OLGIM stage III or IV have a higher gastric cancer risk, and a surveillance endoscopy should be offered to these patients. In this regard, considering the technological advances that make dysplasia visible, it may happen that the updated Sydney system undergoes further evolutions and, ultimately, also the OLGA-OLGIM system.

Considering all, Computer-Aided Diagnosis CNN systems using IEE and Kyoto score should be refined to confirm the diagnosis of *H. pylori* infection and to accurately estimate the risk of gastric cancer. Artificial intelligence, through IEE and what will be in the future, will allow to overcome the problem of subjectivity related to the training and experience of operators[66].

## CONCLUSION

Given that the assessment of a gastritis can be considered complete only when a gastroscopy with M-IEE is performed by an experienced operator, who defines the Kyoto score, performs gastric biopsies, which are evaluated by pathologist who establishes the OLGA-OLGIM stage, it may happen that the artificial intelligence allows to shorten some steps. The M-IEE, especially magnified narrow band imaging and blue laser imaging - bright, has surpassed WLI in sensitivity and specificity for the diagnosis of MA and IM in gastric mucosa; while linked color imaging accurately evaluates all segments of the stomach by searching for endoscopic findings according to the Kyoto classification of gastritis. Artificial intellingence may be able to further support an update of the Kyoto classification of gastritis that should allow to improve the diagnosis of chronic gastritis, precancerous gastric conditions, lesions of the stomach, and early gastric cancer.

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