

Chromoendoscopy for early diagnosis of gastric cancer

Mário Dinis-Ribeiro

Early diagnosis represents the most important measure to decrease gastric cancer mortality. Endoscopists should be trained to perform standardized extremely rigorous observation with a low threshold of suspicion for neoplasia. Together with recent interest in new imaging techniques such as magnification, chromoendoscopy should be considered to represent a simple, safe and inexpensive technique that may be useful in identifying premalignant conditions and minute cancerous lesions, estimating their superficial extent and determining the histological type and submucosal invasion. *Eur J Gastroenterol Hepatol* 18:831–838 © 2006 Lippincott Williams & Wilkins.

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Department of Gastroenterology, Instituto Português de Oncologia 'Francisco Gentil', Porto, Portugal

Correspondence and reprint requests to Mário Dinis-Ribeiro, MD, PhD, Department of Gastroenterology, Instituto Português de Oncologia 'Francisco Gentil', Rua Dr Bernardino de Almeida, 4200-072 Porto, Portugal
Tel/fax: +351 22 508 40 55;
e-mail: mario@med.up.pt

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Introduction

Gastric cancer is the second most lethal cancer in the world [1–3]. Its prognosis is closely related to the stage at diagnosis [4–6]. If diagnosis occurs at an early stage the patient's 5-year survival rate is expected to be higher than 90% [1,5]. Therefore, the early diagnosis of gastric cancer currently represents the most important measure to decrease disease-associated mortality [7].

Early diagnosis can be achieved after screening of the general population [7], during diagnostic procedures in symptomatic or in high-risk individuals' follow-up [8–13], but in all cases, extreme rigour and a standardized endoscopic procedure are required. This is because in the stomach early lesions are often flat or depressed [14–17] and are frequently missed [18–23]. Endoscopic examination is the best method to achieve the early diagnosis of gastric cancer but it shows a false negative rate ranging between 1 and 19% [18]. A low threshold of suspicion is therefore needed as false negative cases seem to be mostly (73%) caused by endoscopists' errors [21].

Furthermore, the conditions that play an important role in gastric carcinogenesis [8,10,13] such as atrophic chronic gastritis and intestinal metaplasia are flat and diffuse. As a result, conventional endoscopy shows both high inter-observer variability and low correlation with histology for their diagnosis [23–31].

The use of ancillary techniques such as chromoendoscopy [32–35] and, in particular, the recent interest and improvement in endoscope imaging technologies with regard to resolution and magnification may help in early detection and therapeutic decision-making in gastric cancer [36–42]. Therefore, we aimed to review the role of both chromoendoscopy and magnification in the early

diagnosis of gastric cancer and of precancerous conditions, which with differential diagnosis and follow-up may also lead to the early diagnosis of gastric cancer.

What should we be looking for?

Definition of early gastric cancer

The Paris consensus [14] integrated the Vienna classification for neoplastic lesions in the gastrointestinal tract [42]. The major groups of intramucosal neoplasia (non-invasive low-grade neoplasia, non-invasive high-grade neoplasia and neoplasia with invasion of the lamina propria) [43] tend to occur in a neoplastic lesion that should be called superficial if its endoscopic appearance suggests that the depth of penetration in the digestive wall is not more than the submucosa [14]. To some extent this corresponds to the term 'early cancer', which suggests a localized tumour with the potential for complete cure after endoscopic resection, i.e. with a low risk of lymph node metastases [4,6,14,15]. Recommendations for endoscopic therapy currently consider both types of lesion and their dimensions in superficial extent.

Endoscopic features of early gastric cancer, classification and interpretation

In Japan, in 1962, the first description of the endoscopic features of early cancers was made, concerning those easily detected at that time: deeply ulcerated and polypoid early cancers. In the 1970s, it also became possible to detect lesions showing features similar to an ulcer scar and those with a 'plateau-like' elevation. More recently, in the 1980s and 1990s, following retrospective studies of patients with rapidly growing cancers from whom endoscopic examination records were reviewed, it was possible to note that faint erythematous or

discoloration changes may correspond to 'gastritis-like' superficial cancers.

In summary, type 0 or early superficial gastric cancer should be classified as (see Fig. 1): protruded (type 0-I) occurring in approximately 3% of cases [14,44,45], and should be identified as that when its thickness represents more than twice that of the normal adjacent mucosa; non-protruded, classified as superficially elevated (type 0-IIa) if its thickness is less than twice that of the normal mucosa; as flat (type 0-IIb) and as the most frequent (78%) depressed type (0-IIc); or as excavated (type 0-III), which represents 2% of cases.

The main relevance of this classification is that it is related to submucosal invasion, which has obvious therapeutic relevance [14-16,19,20].

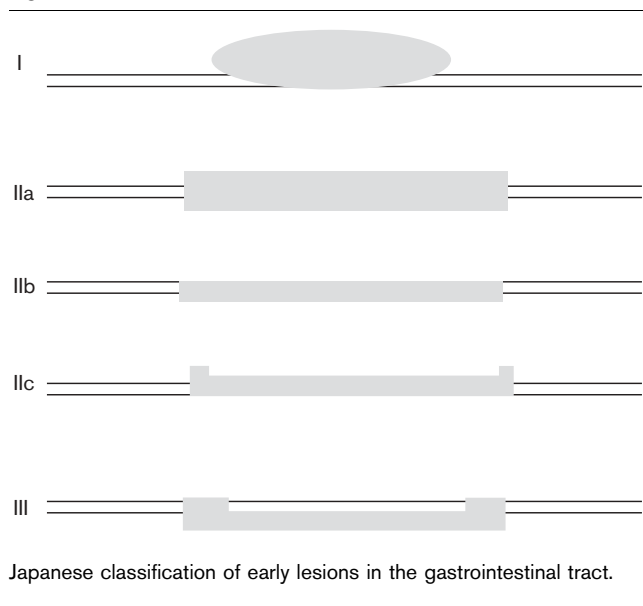
If for protruded lesions, their diameter is reliably related to invasion, in non-polypoid, namely in type 0-IIb and type 0-IIc, several other features (a) of the lesion itself, and (b) of the overlying mucosa and of the demarcation of the depressed area, if they exist, should be clearly observed in the assumptive histological diagnosis of malignancy and invasion. This characterization should mention: (a) the surface structure including the description of the depressed area, namely the presence of protrusion in this area; (b) the presence or absence of a vascular pattern; (c) changes in colour; (d) the absence of a white coating within the depressed area without ulceration; and easy bleeding. It should also be noted (e) if the area of demarcation between the lesion and the surrounding area is well demarcated or ill demarcated and if an irregular saw-tooth pattern at the demarcation of the

depressed area (encroachment) is present; and (f) if marginal elevation exists. Also (g) all changes in the folds such as convergence, tapering, abrupt cessation, clubbing or fusion should be described [16].

In depressed lesions (0-IIc) [14,19], partly or generally amorphous, a deeply red surface with encroachment, clubbing or fusion of the folds is often found in lesions that tend to invade into the submucosa. Furthermore, lesions without ulceration, and with poor distensibility of the wall and linear contour of the wall after inflating the stomach are strongly indicative of submucosal invasion. A white coating in the active stage, a uniformly red surface in the healing stage, uneven differentiation from the surrounding mucosa, multiplicity and a regular radial or linear pattern tend to occur in benign erosions. On the contrary, in depressed excavated lesions the erosion is less flat and has an irregular, uneven surface ranging from finely granular to nodular to amorphous. Type 0-III is also diverse in shape and size, has an irregular arrangement, and shows distinct demarcation, with an irregular depressed surface or encroachment [15-17].

The increasingly recognized 'gastritis-type' 0-IIb, with a prevalence ranging from 3 to 51% may include three types: flat discoloured (usually well demarcated from adjacent mucosa (70%), flat hyperaemic (in relation to Laurèn's intestinal type of adenocarcinoma [46]) poorly differentiated from the adjacent mucosa, or superficially uneven (almost all cases intestinal type). Honmyo *et al.* [47] reported that, beyond the histological type, size, depth of infiltration of neoplasia (most are uneven) and the difference in number of capillaries between cancer and the adjacent mucosa of these lesions influenced the colour changes.

Fig. 1



How can chromoendoscopy help?

With little equipment, dye solutions are applied to the mucosa of the gastrointestinal tract, enhancing the recognition of details not perceivable by purely optical methods [33-35]. Since the early days of endoscopy, various dyes that were already well known in histochemistry with different characteristics have been used: to highlight features and contrast (contrast dyes); to be absorbed by specific epithelia (absorptive or vital dyes); to promote a chemical reaction with specific epithelial secreting cells (reactive dyes).

In the stomach, the most frequently used dyes are indigo carmine, methylene blue and Congo red. In all cases, before spraying dye into the gastric mucosa, this should be cleaned with water and simeticone. When available, pronase should be given to the patient, as demonstrated in a randomized controlled trial [48], to improve the observation of the gastric mucosa.

Indigo carmine, in an aqueous solution of 0.1–1.0%, is easily sprayed into the mucosa and produces a colour contrast to the reddish mucosa. In particular, the deep blue colour fills the bottom of flat ulcers, erosions, folds and pits, and specifically accentuates the depressed type of early forms of gastric cancer. It is a safe, water-soluble, inexpensive dye, with no severe side-effects.

Its clear benefit in increasing the identification of lesions has never been confirmed by randomized trials. However, extensive clinical practice in endoscopic centres worldwide, namely in Japan [49–51], and a single prospective study [49] (the aim of which was to evaluate the comparative results of video against fibre endoscopy) showed that the use of indigo carmine as a dye increases the detection and identification of significant lesions (see Fig. 2).

Generally, there is no indication for routine pangastric chromoendoscopy. Instead, dye should be sprayed over subtle areas with colour differential, slight haemorrhage or friability [49–51] and small areas with a loss of vascular pattern. This will enable the endoscopist to highlight type 0–IIb or to demarcate types 0–IIc or III early cancers. The above-mentioned features, considered basic in all descriptions of these lesions, are better seen after indigo carmine staining.

Methylene blue is taken up by the active absorbent tissue of the small intestine and colonic mucosa and particularly stains intestinal metaplasia in the oesophagus and stomach [32,52]. It requires that the mucosa has previously been sprayed with a mucolytic, either pronase or 10% acetylcysteine, solution. It adds approximately 5–7 min to the procedure, because after the 2 min needed for mucolytic action, methylene blue is sprayed and approximately 3 min later, the mucosa is vigorously cleaned with water or saline solution, to permit further observation. An important problem is the endpoint of staining. Although this is not defined, from the study by Fennerty *et al.* [52] and our own experience, methylene blue staining should be considered finished when the endoscopist considers that all gastric mucosa has been put into contact with dye, and that the blue colour is stable in terms of intensity, and the number and dimensions of areas of the mucosa have been covered (see Fig. 3). At the end, we may expect to observe the mucosa to be ‘subtle focal’, ‘subtle diffuse’, ‘prominent focal’ or ‘prominent diffuse’ stained or on the contrary with no stain: ‘negative’.

Methylene blue has virtually no side-effects, although the patient should be told that the urine and stool sometimes turns green. DNA damage after methylene blue chromoendoscopy was recently reported in a cross-sectional study [53]. However, it is currently accepted that a

chronic exposure to a mutagenic agent is necessary to have an effect on the onset and aetiopathogenesis of cancer and precancerous lesions. Therefore, it is questionable whether a short exposure to methylene blue is sufficient to accelerate carcinogenesis in the gastrointestinal tract. The incidence rates of patients with atrophy and intestinal metaplasia developing into dysplasia have been no more than expected in most studies, including our own cohort of patients that we have followed since 2001 (unpublished data). We therefore argue that serious concerns in clinical practice about the use of methylene blue are not justified.

A few reports have also studied the impact of this type of dye in the diagnosis of *Helicobacter pylori* [54,55]. However, they do not clarify the relative role of staining and the previous well-known difficulty in diagnosing *H. pylori* infection in areas of intestinal metaplasia [56,57].

Congo red, in a 0.3% bicarbonate solution, sprayed on the gastric mucosa will identify acid-secreting gastric cells. It causes the colour in the mucosal regions to change from red to dark blue.

In consecutive application with methylene blue, mucosal areas altered by tumours are bleached out within minutes [58–60]. Although showing good validity for the diagnosis of atrophy (with an estimated sensitivity of 100% and a positive predictive value of 90%), it involves the stimulation of acid secretion by parenteric (intramuscular or intravenous) pentagastrin injection, and is therefore extremely time consuming and cumbersome. Therefore, most recent studies have focused on its use for the assessment of the completeness of vagotomy [61,62], but even then it is seldom used and is not current practice in most centres worldwide.

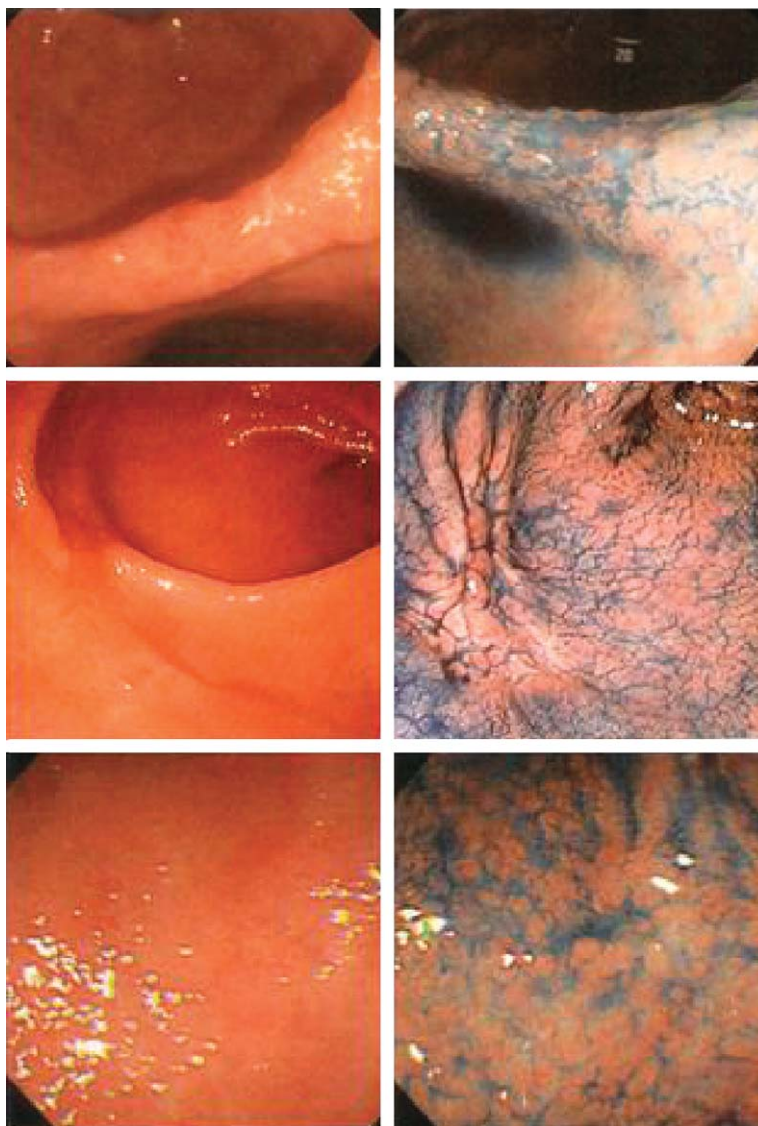
Chromoendoscopy with indigo carmine can therefore be considered to be simple, inexpensive and probably useful for the identification of lesions. Other types of dyes may be considered in selected cases such as high-risk patients (see below) or specific situations such as postsurgery assessment.

Is there a role for endoscopic magnification in early gastric cancer diagnosis?

Recent models of endoscopes have the capability of high-quality digital imaging in terms of resolution, colour reproduction, contrast and structure enhancement. Several studies have considered magnification and high-resolution endoscopes in conjunction with chromoendoscopy.

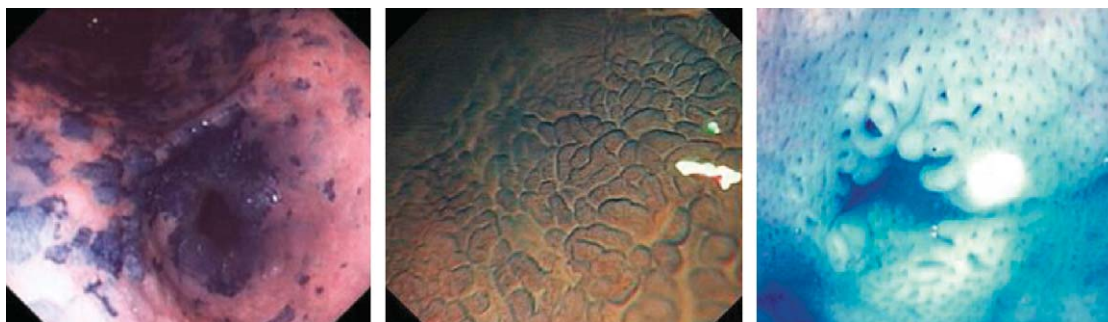
There are two distinct [19,34,36] applications for magnification endoscopy with optical zooming. It may

Fig. 2



Chromoendoscopy with indigo carmine enhancing the identification of type IIc superficial lesions in the incisura and proximal antrum and type IIb in the lesser curvature of the antrum (from above to bottom).

Fig. 3



Chromoendoscopy with methylene blue. From left to right, antrum and incisura view after methylene blue (1%) staining resulting in prominent focal staining according to classification of Fennerty *et al.* [52]; magnified view (Olympus Q240Z, ~105 ×) with a type IIF pattern and a focal area with loss of mucosal pattern (type III) (with dysplasia), according to Dinis-Ribeiro description.

use mucosal ‘transparency’ for exploration of the altered microvasculature network characteristics of neoplastic lesions across the translucent unstained epithelium. This can be obtained without chromoscopy or with the recently described acetic acid. Furthermore, with the help of ‘contrast’ chromoendoscopy, it can effectively distinguish between the different architectures of various epithelia, and it can analyse the degree of surface disorganization in neoplastic lesions [63].

Magnification endoscopes are equipped with CCD chips that allow [36] images to be built with 100 000–300 000 individual pixels (or picture elements). High-resolution endoscopes are capable of discriminating objects 10–71 µm in diameter, i.e. two to 10 times greater than the naked eye. Although closely related (at the same level of magnification, high-resolution endoscopes provide a more detailed picture), magnification has a distinct quality. High-resolution imaging improves the ability to discriminate detail, whereas magnification is closely related, with optical zooming and enlargement of the image, which in turn is different from electronic manipulation and zooming, which beyond certain levels loses quality [36]. Endoscopic magnification (1.5–105 ×) is made available by controlling the focal distance of a movable motor-driven lens.

Up to now, no complications specifically attributed to the use of high-resolution endoscopes beyond those attributable to the endoscopic techniques themselves have been noted.

Tajiri *et al.* [64], using magnification endoscopy and indigo carmine, considered this procedure to be very useful in predicting histological diagnosis during endoscopic procedures. Separating the lesions according to type (depressed versus elevated lesions) and size (10 mm cut-off), the authors found differences in diagnostic accuracy of between 3 and 36%, favouring magnification in comparison with conventional endoscopy. Sensitivity for lesions as severe as adenoma was 96%, and specificity considering erosion and ulcers as a false-positive diagnosis was 95%. The authors also stressed the relevance that this procedure may have in minute flat ‘gastritis-like’ lesions.

Furthermore, a magnifying endoscope may be useful for assessing or trying to identify the histological type of gastric cancer (differentiated versus undifferentiated). Sakaki [65] reported that structural atypia (termed ‘fine C pattern’) is present in differentiated cancer; whereas undifferentiated cancer shows an irregular (D) pattern. No assessment was made, however, concerning the reliability of this classification.

According to the colour and homogeneity of mucosal features, our group described three groups (I, II and III)

and two subgroups (IIE and IIF) of patterns using magnification chromoendoscopy in gastric mucosa [66]. Group I was defined by mucosa showing no change in colour after staining with methylene blue, and a regular mucosal pattern. Group II was defined by the mucosa staining blue and the presence of a regular pattern. IIE included areas of mucosa with blue irregular marks (initially called IIA) or blue round and tubular pits (IIB); and IIF was defined by blue villi (IIC) or blue small pits (IID) being present in the observed mucosa. Group III (‘dysplastic mucosa’) was defined by no clear change in colour (heterogeneous) and no clear pattern being noticeable. The so-called I, II and III patterns may be comparable with other classifications in the columnar lined upper gastrointestinal tract.

This description presents excellent intra-observer agreement (Cohen’s kappa 0.86) and substantial inter-observer agreement, for classification into groups. As for the classification including subgroups (I versus IIE versus IIF versus III) inter-observer agreement was estimated to be moderate both in stationary images and on the multiple observations of videos [67]. This classification showed a global validity of 83% [95% confidence interval (CI) 74–91%] for dysplasia. Of great importance is the negative predictive value of 100% (95% CI 99–100%) or the very low negative likelihood ratio for dysplasia [0.04 (0.01–0.26)], which is of major importance in gastric mucosa minute lesions.

In summary, if chromoendoscopy helps in identifying minute lesions and in the characterization of early lesions, magnification fulfils the following task: it may clarify the superficial extent of lesions and assess their histological type.

In the diagnosis of pre-cancerous conditions is chromoendoscopy with or without magnification useful?

The follow-up of individuals with lesions associated with gastric cancer may lead to early cancer diagnosis [13]. However, no such management model has yet been proposed. This could partly be justified by the low validity and reliability of conventional endoscopic techniques for atrophic chronic gastritis and intestinal metaplasia. Furthermore, as stated above, in type IIb early gastric cancer, small areas of changes in the mucosa may easily be misinterpreted as ‘gastritis’ and therefore missed during follow-up studies.

Atkins and Benedict [25] showed that the classification of the appearance of the gastric mucosa and folds into three types of endoscopic gastritis: superficial, atrophic and hypertrophic had a specificity of 53%. Heinkel [26] reported normal endoscopic changes (sensitivity of 76%) in 24% of patients with atrophic chronic gastritis. In 1984,

after the attempt of Myren and Serck-Hanssen [27], one decade earlier, to diagnose atrophic gastritis endoscopically, through a 'visible vascular pattern in thin mucosa', Sauerbruch *et al.* [28] described the results of a simultaneous but independent diagnostic endoscopic examination in 152 consecutive patients in whom diagnostic endoscopy was performed. Beyond focal lesions, the proportion of agreement was greater than 80%, both for the presence of submucosal vessels [sensitivity for atrophy varying from 50 to 100% (antrum to corpus), specificity of 81–95% and positive predictive value of 22–67%], and for the decrease in folding (sensitivity 50%, specificity 92% and predictive positive value 27%). The authors were able to conclude that, beyond previously mentioned features, namely visible blood vessels [29], most of the usual features described in conventional endoscopy are of little diagnostic value for a diagnosis of histological gastritis. Laine *et al.* [30] found moderate agreement on endoscopic descriptions for the diagnosis of chronic gastritis made in Sydney [31], namely for prominent *areae gastricae* in the body of the stomach ($k = 0.49$), nodularity in the body ($k = 0.65$) and antral nodularity ($k = 0.68$). Furthermore, Belair *et al.* [32] described areas under the receiver operating curves of 0.65 for the diagnosis of gastritis, under the same criteria.

Therefore, with the exception of atrophic vascularization, most studies found suboptimal validity (relation with histology) and, as assessed in only a few studies, unsatisfactory reliability for conventional descriptions of 'gastritis'.

With regard to intestinal metaplasia in the stomach, using conventional endoscopy, a single description exists [56]. Numerous, evenly distributed, small (1 mm) white elevations separated by pale orange mucosa were related to the presence of intestinal metaplasia. No reliability evaluation was performed.

The first reports of the use of magnification chromoendoscopy for the description of gastric mucosa were performed by Sakaki *et al.* [68]. Using Congo red, a classification of normal mucosa was described consisting of the observation of gastric pits: A (dotted), B (short-linear), C (striped), D (circular) or mixed patterns (AB, BC and CD).

Yagi and colleagues [69,70] described the 'regular arrangement of collecting venules' named after the dotted redness shown in magnification. This feature showed a sensitivity of 94% and a specificity of 96% for the 'absence of gastritis induced by *H. pylori*'. A 'well-defined ridge pattern', when the mucosa ridges were arranged regularly and closely and minute points could be seen in each ridge, was related to normal antral mucosa (sensitivity 55%, specificity 100%). On the other hand, if

the ridges are separated and are not clearly distinguishable for the white amorphous mucosa between them, a so-called 'ill-defined ridge pattern' may include gastritis with *H. pylori*.

Recently, Kim *et al.* [71] aimed at identifying histological gastritis through magnification with indigo carmine. They described four patterns: pinpoint pits on the flat field (type 1); regular, trabecular ridge pattern or a regular, flat granular pattern (type 2); irregular or coarse granular structure (type 3); and prominent clubbing (villous) or papillary pattern (type 4). Type 1 would correspond to fundic normal mucosa, type 2 was related to gastritis or normal with pyloric glands, types 3 and 4 would be able to diagnose gastritis and also intestinal metaplasia (present in 44% of cases with these patterns).

More interestingly, the authors also compared their observations with conventional endoscopy, showing an increase both in sensitivity and specificity (96 and 74% for magnification endoscopy versus 66 and 54% for conventional). Global accuracy was 84%.

The size and the presence of inflammation in the stomach, as described by other authors in other organs, should be limitations to chromoendoscopy [38].

However, our own results [66,67] were consistent with those previously mentioned by others. In our study we found a validity of 82% (95% CI 68–95%) for a diagnosis of intestinal metaplasia.

Our group I may include those defined by Sakaki *et al.* [68] or types 1 and 2 from Kim *et al.* [71]. Furthermore, the description of Yagi *et al.* [69,70] of normal and 'gastritis'-afflicted mucosa may be included in our group I; their 'regular arrangement of collecting venules' and 'well-defined ridge pattern' may correspond to our IA and IB, whereas 'ill-defined ridge pattern' may correspond to our IC or eventually ID.

Also group II considers the absorptive capacity of intestinalized epithelium, through cell membrane into the cytoplasm by an unknown mechanism, and also takes into consideration the morphological pattern well grounded on ultrastructural features [33]. These may also be comparable, although with types 3 and 4 of the classification of Kim *et al.* [71].

Furthermore, this classification identifies the 'patternless' as the most severe of the patterns. A previous explanation for the disappearance or heterogeneity of staining in dysplasia and a loss of pattern in magnification was given [33]. In dysplastic epithelium, by decreasing in cytoplasm (increase in nuclear to cytoplasm ratio) and by a decrease in the number of goblet cells a loss of blue

colour is noted. A further loss of pattern may be related to disorganization in these lesions.

In most recent studies, reliability was assessed, and substantial to excellent results were noted. These findings need standardization [42], together with other descriptions in columnar lined epithelium in the upper gastrointestinal tract. As most studies report the results of observations in non-selected groups of patients, the clinical usefulness of this procedure can be anticipated.

Therefore, in relation to histopathological standards, magnification chromoendoscopy may be useful in reducing sampling error in the diagnosis of intestinal metaplasia and the exclusion of dysplasia, which may be of great importance in the follow-up of these patients with an early diagnosis of gastric cancer.

In conclusion, it is possible to conceive simple, reliable, self-explanatory and easy to learn endoscopic classifications with good relationships with histopathological results.

Conclusion

It has been felt that western endoscopists do not appreciate the routine use of chromoendoscopy. However, it has been shown that chromoendoscopy, at least with the use of indigo carmine, is a simple technique that may be helpful for highlighting and the identification of subtypes of neoplastic lesions, namely types 0–II in which no lesion is observed without chromoendoscopy. Furthermore, endoscopic therapy (mucosectomy) has become routine for early malignant changes in the gastrointestinal tract, and accurate diagnosis and a detailed description of such changes are essential prerequisites.

Although the standardization of magnification patterns of with observed changes in the gastric mucosa is desirable, studies tend to mention the same features. We may assume therefore that its use should be considered, if available, for further characterization in histological assessment and lateral extension, namely in therapy decisions.

Also in follow-up studies, other dyes such as methylene blue and magnification may be used in high-risk patients, as their follow-up may represent an effective model for the early diagnosis of gastric cancer.

In summary, in all procedures, endoscopists should attempt to identify the presence of an area of the mucosa that is slightly discoloured (pale or red), an irregular microvascular network and a slight elevation or depression. This should be followed by chromoendoscopy to help with the description of the lesion, probably using indigo carmine. With increasing familiarity with pattern

classification, magnification may also result in a very useful procedure.

Conflict of interest

None declared.

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