# Endoscopic Examination: a Present and Future Challenge

Boeriu Alina[1], Dobru Daniela[1], Mocan Simona[2], Pascarenco Ofelia[3], Stoian M[4], Boeriu C[5]

[1] Department of Gastroenterology, University of Medicine and Pharmacy, Tîrgu Mureş, Romania
[2] Department of Pathology, County Emergency Hospital, Tîrgu Mureş, Romania
[3] Department of Gastroenterology, County Emergency Hospital, Tîrgu Mureş, Romania
[4] Intensive Care Department, County Emergency Hospital, Tîrgu Mureş, Romania
[5] Emergency Department, University of Medicine and Pharmacy, Tîrgu Mureş, Romania

The detection and surveillance of patients with premalignant gastric lesions could lead to early detection and treatment of gastric cancer. These lesions are mostly diagnosed in random biopsy samples obtained during conventional endoscopy. New endoscopic techniques, such as magnification endoscopy, may help the detection of neoplastic lesions. In this case series, we intended to emphasize the current problems in the detection and surveillance of gastric neoplasic lesions in clinical practice. Four cases with gastritis-like appearance on conventional endoscopy were identified with gastric dysplasia or carcinoma on histopathologic evaluation. We discussed the subjective interpretation of endoscopic findings, the challenges in the surveillance of low-grade dysplasia and the contribution of magnifying endoscopy on diagnostic accuracy. The performance of endoscopic examination and surveillance could be improved by magnified chromoendoscopy with targeted biopsies. An understanding of diagnostic challenges of gastric dysplasia is crucial in clinical management.

**Keywords:** magnifying chromoendoscopy, detection, surveillance, dysplasia, gastric cancer

## Introduction

Gastric cancer remains an important cause of death that is, unfortunately, frequently detected only when it has reached an advanced, incurable stage. Patients whose malignancy is detected early have a significantly better prognosis. A progression of premalignant lesions has been identified [1] and many studies have emphasized the importance of early detection and subsequent endoscopic surveillance of these lesions. [2] The diagnosis of premalignant lesions and gastric cancer on conventional endoscopy is frequently impaired by subjective interpretation of endoscopic aspects and by poor correlation between these and histologic findings.

Surveillance gastroscopy has suboptimal sensitivity for detecting dysplasia [3]. A protocol with multiple biopsies is still advocated to detect these invisible lesions [4]. The use of novel endoscopic imaging technologies, such as magnifying endoscopy, permits an analysis of the mucosal architecture and increases the chance of detecting dysplastic and malignant lesions by targeted biopsies. Even so, the diagnosis of gastric neoplastic lesions can be challenging due to the large surface area that has to be examined. This is especially true in patients without remarkable endoscopic changes. In the present article we present several clinical scenarios that elucidate these issues.

## Material and methods

In this paper we present four cases with gastritis-like appearance at conventional endoscopy in which magnifying endoscopy and histopathological examination revealed premalignant and malignant changes in gastric mucosa. This raises important questions about the proper evaluation of the risk of the patients and the ideal method for detection and subsequent surveillance of neoplastic lesions.

## Case 1 and 2: low-grade dysplasia (LGD)

Two female patients were investigated with conventional endoscopy for dyspeptic complaints. We detected mucosal changes in the antral area: nodular deformity (Figure

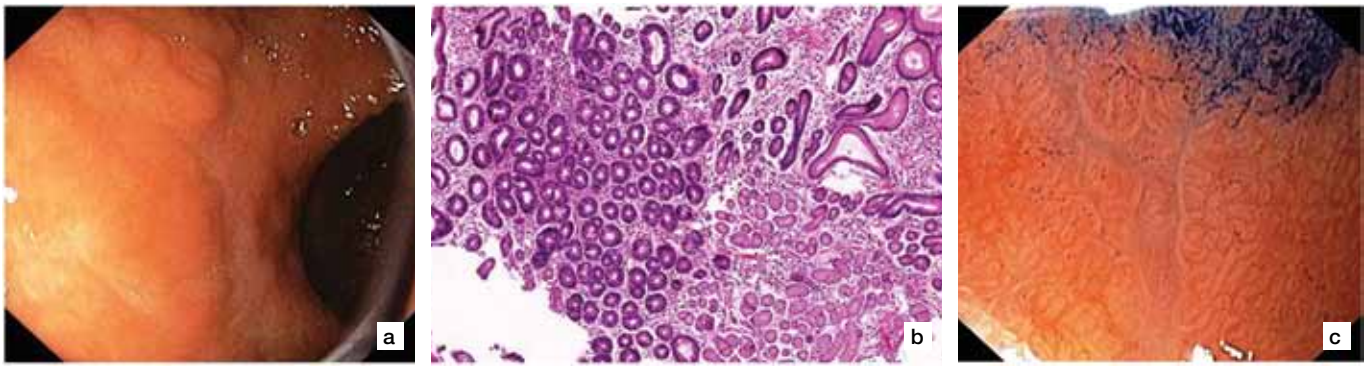


**Fig. 1. Conventional endoscopic view: nodular appearance in antral area (a); Histopathological findings of a biopsied specimen from the antral mucosa revealed LGD (b); Endoscopic high magnification image of antral mucosa showed areas with the disappearance of the regular SECN pattern (c).**

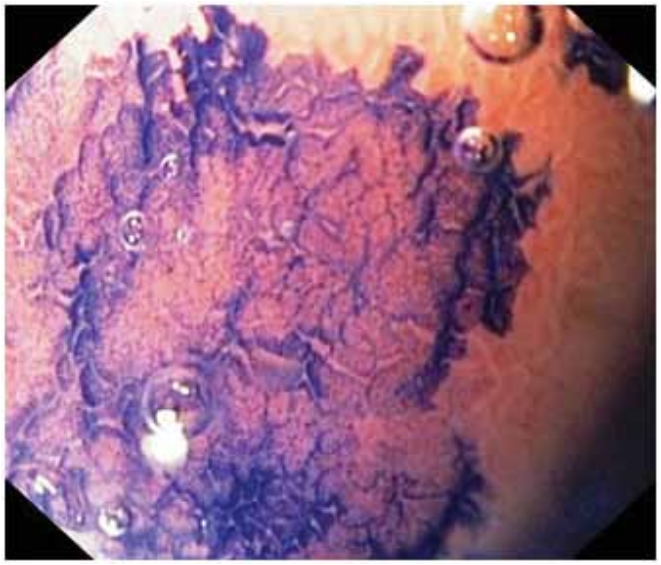

Fig. 2. Stained areas showed tubular pit pattern on magnification

1a), erythema and erosions. Biopsies from the modified mucosa were obtained. Histological evaluation revealed LGD (Figure 1b). The biopsy specimens were diagnosed according to the Vienna classification for gastrointestinal epithelial neoplasia [5]. According to the international guidelines, patient with LGD are currently advised to undergo periodic endoscopic surveillance for early detection of progression [6]. We prescribed therapy with proton pump inhibitors (PPI) and we recommended regular surveillance. After three months, we performed magnification chromoendoscopy with 0.5% methylene blue solution in order to identify not only the LGD, but also to detect any possible abnormality in other parts of the stomach. We obtained heterogeneous staining of antral mucosa and small homogenous dark blue areas. We magnified the gastric mucosa, especially the antral region. In one case, we detected normal antral mucosa, with regular pattern: coil-shaped sub-epithelial capillary network (SECN). Magnified endoscopic findings of the gastric angulus, with a nodular appearance by conventional examination, showed the disappearance of the regular SECN pattern (Figure 1c). The histopathological examination of a biopsied specimen from the lesion showed only chronic gastritis with intestinal metaplasia. In the second case, we detected normal SECN pattern in unstained areas. In dark blue stained areas we detected tubular patterns, as shown in Figure 2. Areas exhibiting tubular pattern yielded intestinal metaplasia in biopsy specimens. In both cases, we failed to detect LGD in follow-up endoscopic examinations.

## Case 3: high-grade dysplasia (HGD)

A 78 years old male patient presented with epigastric discomfort, nausea, weight loss over the past 3 months. We performed conventional endoscopy. In the antral area we detected small reddened lesions and erosions, congestion and friability (Figure 3a). We took biopsies from modified gastric mucosa and initiated antisecretory therapy. One week after, we performed magnifying endoscopy after instillation of 1.5% acetic acid. We detected smaller erosions in antral area and erythema. It was not possible to differentiate whether these lesions are due to gastritis or gastric neoplasia by conventional endoscopic findings alone. Under magnification, antral mucosa presented an irregular pattern that replaced the normal coil-shaped pattern. We also detected abnormal microvessels and variation of vessel caliber (Figure 3b). Histopathologic examination showed HGD in biopsy specimens from antral mucosa. We recommended surgical treatment in this case. A gastric resection was performed and the gastrectomy specimen was examined at Department of Pathology. The histological examination of resected specimen showed the presence of HGD (Figure 3c).

## Case 4: gastric carcinoma

A 51 year old man was admitted in our department with abdominal discomfort and distension. Abdominal ultrasound examination reveled ascites. Computed tomography of the abdomen and pelvis demonstrated intraabdominal fluid and peritoneal thickening. Conventional upper endoscopic examination reveled erythema with mosaic pattern in subcardial region. We took biopsies from modified area and prescribed PPI therapy for this patient. Histological examination showed signet ring-cell carcinoma. Figures

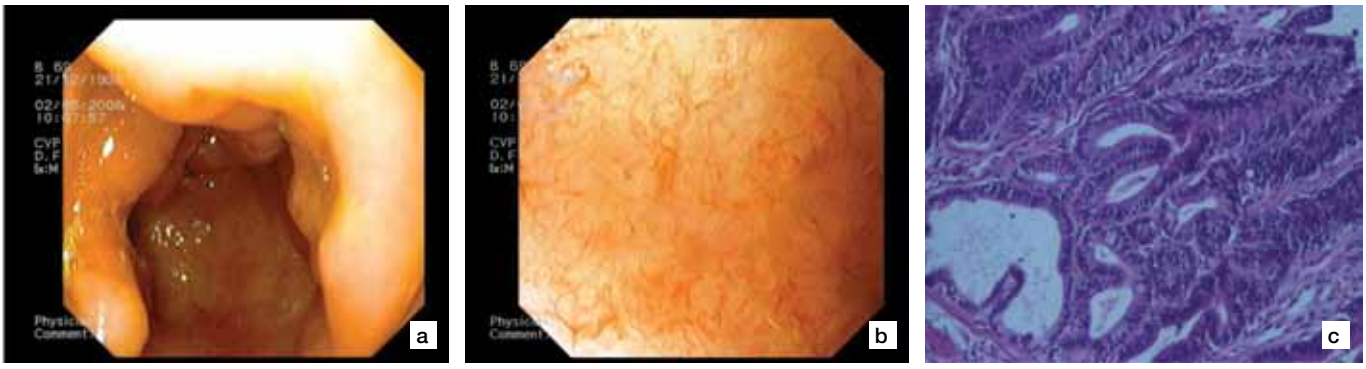


Fig. 3. Conventional endoscopic findings showed small reddened lesions and erosions in the antral area (a); Endoscopic high magnification image of antral mucosa after acetic acid application showed abnormal microvessels: irregular length, caliber and distribution (b); Histological findings of the surgical resected specimen demonstrated HGD (c).

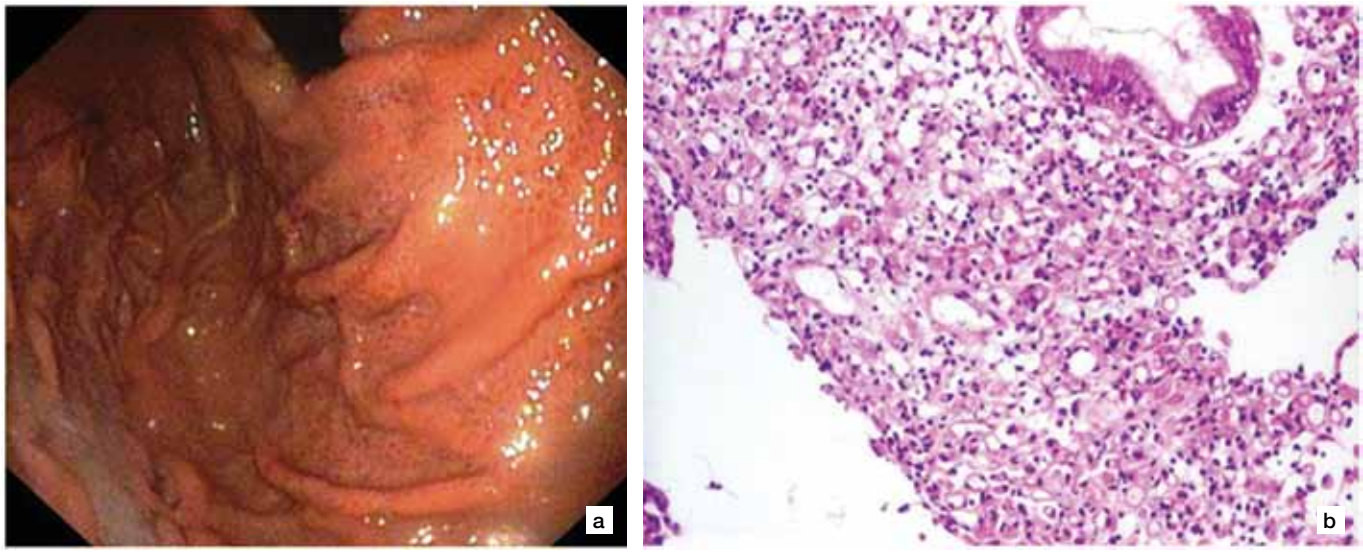


**Fig. 4. Conventional endoscopic view: erithema in subcardial area (a); Histological findings of a biopsied specimen from subcardial area showed signet ring-cell carcinoma (b).**

4 a, b show the conventional endoscopic findings and the histopathological findings. In the absence of a clear lesion, in order to rule out a possible error, we performed additional gastroscopies with multiple biopsies. No endoscopic lesions were identified in the presence of antisecretory therapy. Blind biopsies from normal appearing mucosa showed chronic gastritis. No tumor tissue was found at histological evaluation of random biopsies. At that time, we could not perform magnifying endoscopy for a pit pattern evaluation and targeted biopsies. We found no evidence of colonic lesions by colonoscopy. A laparoscopy with evaluation of peritoneal surfaces was performed and revealed peritoneal metastases. Peritoneal biopsies confirmed the initial histological diagnosis: signet ring-cell carcinoma.

## Discussions

The diagnosis of gastric premalignant lesions and the detection of gastric cancer depend on a careful examination of gastric mucosa by conventional endoscopy and histopathologic evaluation of many biopsy specimens. For this reason some alternative diagnostic procedures have been developed with better visualization of mucosal structure and vascularization. Magnification chromoendoscopy allows more precise diagnosis of premalignant and malignant lesions [7, 8].

Dysplasia is the main step in gastric cancer development, and its detection is crucial in the evaluation of patient's cancer risk [9]. The diagnosis of LGD is associated with significant inter-observer variability [4, 9]. We have discussed the difficulties in the detection and surveillance of LGD, and even of more advanced lesions, in the absence of a macroscopic change in the gastric mucosa. In order to improve the detection of LGD, we used magnifying chromoendoscopy, but we failed to detect the lesion in the antral area in two cases after a three months follow-up period. This could represent true regression of LGD or sampling error.

The surveillance and management of LGD remains controversial, especially when follow-up endoscopies with biopsies or resected mucosal specimens are negative for dysplasia. In a recent study that included 293 patients with gastric LGD, Kim et al. reported fifteen lesions (5.5%) with LGD on initial histological evaluation by forceps biopsy that turned out to be non-neoplastic after endoscopic mucosal resection (EMR). The authors offered a possible explanation for this discrepancy: the EMR specimen did not include the epithelial dysplasia or the areas of dysplasia were so small that they were removed by the forceps biopsy. On the other hand, 51 patients (18.7%) showed an upgraded histology after endoscopic resection (EMR diagnosis showed histology of more malignant potential) [10]. In the study reported by Kim et al., the authors showed discrepancies between histolopathological evaluation by forceps biopsy and the mucosal samples obtained by endoscopic mucosal resection, especially in case of LGD [11].

In conclusion, the current standards in the detection and management of patients with gastric LGD have limitations and still require further research to improve their efficacy. The critical issues to be addressed are: 1) failure to detect an advanced lesion and 2) improper localization.

Irregular microvessels and the disappearance of the normal pit pattern are changes detected in the antral area in our patient with HGD. Niwa et al. reported small regular pattern, irregular patterns, as well as a lack of visible structure and abnormal vessels in early gastric cancers [12].

The fourth patient investigated with conventional endoscopy showed no particularly changes in the gastric mucosa. We obtained histologic discrepancies between forceps biopsy specimens at the initial endoscopy and subsequent endoscopies. Because of the lack of a clear endoscopic lesion, random biopsies failed to confirm the initial diagnosis, even in the setting of advanced carcinoma. Recently, Solis-Munoz et al. described the case of a 55 year old male without endoscopic lesions who demonstrated in one bi-

opsy sample obtained from the body of the stomach intramucosal signet ring-cell adenocarcinoma. Further gastroscopies and biopsies did not confirm the initial diagnosis during a follow-up period of four years. A possible explanation for this is that the focus of tumor cells was eliminated with the forceps biopsy [13].

In the absence of a circumscribed endoscopic lesion, the detection of dysplasia and even carcinoma can be difficult. The pit pattern evaluation of a large area like the entire antral mucosa can be a challenge from the perspective of time, technique and inter-observer agreement. These methods require further revisions in order to improve standardization and diagnostic accuracy.

## Conclusions

There are difficulties in the management of LGD, due to the inter-observer variability in the interpretation of dysplasia. Even more advanced lesions can be difficult to detect because of a "benign" endoscopic appearance, especially after PPI administration. Sampling errors from forceps biopsies, discrepancies between endoscopic appearance and histological findings, as well as discrepancies between successive examinations during the surveillance period, are continuous challenges in clinical practice. The new endoscopic techniques are providing the endoscopist with the opportunity both to diagnosis gastric cancer earlier and to develop better surveillance strategies for patients with premalignant lesions.

## Acknowledgement

This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU 60782.

## References

1. Correa P – Human gastric carcinogenesis: a multistep and multifactorial process – First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992, 15(52): 6735–6740.
2. De Vries AC, Haringsma J, Kuipers EJ – The detection, surveillance and treatment of premalignant gastric lesions related to Helicobacter pylori infection. Helicobacter 2007, 12: 1–15.
3. Rugge M, Cassaro M, Di Mario F et al. – The long term outcome of gastric non-invasive neoplasia. Gut 2003, 52: 1111–1116.
4. Noffsinger A and Waxman I – Preinvasive neoplasia in the stomach: Diagnosis and treatment. Clinical Gastroenterology and Hepatology 2007, 5: 1018–1023.
5. Dixon MF – Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 2002, 51: 130–131.
6. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointestinal Endoscopy 2006, 63(4): 570–580.
7. Areia M, Amaro P, Dinis-Ribeiro M, Cipriano MA, Marinho C, et al. – External validation of a classification for methylene blue magnification chromoendoscopy in premalignant gastric lesions. Gastrointestinal Endoscopy 2008, 67(7): 1011–1018.
8. Otsuka Y, Niwa Y, Ohmiya N, et al. – Usefulness of magnifying endoscopy in the diagnosis of early gastric cancer. Endoscopy 2004, 36: 165–169.
9. Sharma P – Low-grade dysplasia in Barrett's esophagus. Gastroenterology 2004, 127: 1233–1238.
10. Kim YJ, Park JC, Kim JH, Shin SK, Lee SK, Lee YC, Chung JB – Histologic diagnosis based on forceps biopsy is not adequate for determining endoscopic treatment of gastric adenomatous lesions. Endoscopy 2010, 42: 620–626.
11. Kim ES, Jeon SW, Park SY, Park YD, Chung YJ, et al. – Where has the tumor gone? The characteristics of cases of negative pathologic diagnosis after endoscopic mucosal resection. Endoscopy 2009, 41: 739–745.
12. Niwa Y, Ohashi A, Miyahara R, Ohmiya N and Goto H – Differential diagnosis of gastric lesions by magnifying endoscopy. Digestive Endoscopy 2005, 17(Suppl.): S20–S22.
13. Solis-Munoz P, Solis-Herruzo JA, Lopez-Alonso G, Colina-Ruizdelgado F, Munoz-Yague T – Unfound gastric signet ring-cell adenocarcinoma after gastric biopsy. Endoscopy 2010, 42: 429