How are we addressing gastric intestinal metaplasia?

Raúl A. Cañadas Garrido, MD[1]

1 Internist and Gastroenterologist at Hospital Universitario San Ignacio at the Pontificia Universidad Javeriana, Postgraduate Coordinator of Gastroenterology at the Pontificia Universidad Javeriana, Chief of Gastroenterology at Marly Clinic in Bogota, Colombia

Received: 10-11-12
Accepted: 21-11-12

The increasing sensitization of Colombian gastroenterologists to detection of early gastric cancer is important not only for what it represents for patients prognoses but because of the therapeutic alternatives it opens the door to. These include endoscopic surgery which is less invasive than the already known and accepted surgical treatment with intent to heal.

It is clear for everyone that gastric cancer is still a public health problem and that most patients are diagnosed in advanced stages when there is rarely any option of healing. This makes us look back to the essential, back to screening programs and monitoring of high risk groups, and therefore back to identification of precancerous stages.

The contribution of Dr. Pelayo Correa in describing the pathogenic sequence of intestinal gastric cancer, now accepted worldwide, shows how normal gastric mucosa, when confronted with environmental or hereditary factors, can evolve into superficial chronic gastritis, dysplasia and adenocarcinoma. It passes through intermediate stages such as atrophy and intestinal metaplasia which are considered to be preneoplastic stages, and then it evolves into gastric adenocarcinoma. The literature, however, is still uncertain regarding this final step.

Here is where important questions begin to arise, "Which is more important for monitoring, keeping an eye on atrophy? Or watching the metaplasia?"

In clinical practice we frequently show concern when monitoring metaplasia, but we do not look beyond or delve into the meaning of the term and its physiological and pathogenic implications. We know something related to its natural history, we perceive that the sequence leading to neoplasia may be up to 10 years (1), but we are unaware of how it evolves in the intermediate stages.

Helicobacter Pylori is known to produce chronic gastritis that may lead to reduction or loss of the glandular component leading to atrophy and intestinal metaplasia (IM). This in turn predisposes the patient to the appearance of gastric cancer. Helicobacter Pylori plays an essential role in this profession and was classified as a type I carcinogen in 1994 by the World Health Organization. The combination of a virulent organism and a genetically susceptible host is considered to be associated with greater chronic inflammation and faster progression towards gastric cancer. CagA+ strains are aggressive in infected individuals increasing the risk of gastric neoplasia by 1.64 times. Now, it has been established that atrophy may increase risk of gastric cancer due to the mechanisms of acidic hyposecretion, increased pH and creation of an environment that favors growth of anaerobic flora and which facilitates conversion into nitroso compounds directly involved in the mechanism of carcinogenesis. This should alerts us so that if we

already have metaplasia in mind, we will worry just as much about the atrophy.

In addition, it is fundamental to remember the following concept: eradication of Helicobacter Pylori heals non-atrophic chronic gastritis and may allow partial regression of atrophic gastritis, but eradication does not seem to reverse metaplasia in patients with intestinal metaplasia even though it may slow its progression towards neoplasia and therefore decrease its evolution towards cancer which is why its eradication is recommended (2).

The reasons follow-ups are recommended are our understandings that atrophy and intestinal metaplasia are persistent lesions and that patients with antral atrophy in the gastric body have a greater risk of developing neoplastic regions which is why.

I will analyze these and other worries in this editorial, but not without first acknowledging the groups at the Reina Sofia Clinic and the Colombia University Clinic for having made the effort to search for the fundamental through identification of precancerous lesions in our population, for attempting to solve questions not yet elucidated in the literature, and for desiring to understand our population's need for early identification of pre-neoplastic stages since this is where prevention, which we always mention but scarcely apply, is born.

Regarding current recommendations for handling precancerous gastric lesions, I am obliged to mention the study published in Endoscopy in January 2012. In my opinion this is required reading for the gastroenterologist, gastrointestinal surgeon, internist and all of us who partake in the active study and management of gastric cancer, its precursor factors and precancerous stages. The article: "*Handling lesions and precancerous conditions in the stomach: Guides of the European Society of Gastrointestinal Endoscopy (ESGE), Helicobacter Study Group (EHSG), European Society of pathology (ESP) and the Portuguese Society of digestive Endoscopy (SPED)*" creates consensus guidelines based on the best available evidence even though it leaves the window open for future contributions in areas yet to be defined (3).

When this consensus is studied, it is satisfactory to find Colombian studies that focus on preventive aspect of pathologies and the detection of early lesions. Consequently, I will mention some specific issues in this editorial which are important to highlight in the European consensus. In our environment, a country with a high incidence of gastric cancer, we lack evidence based for monitoring patterns, particularly patterns in precancerous stages.

In general, the article "*Correlation of Endoscopic and Histological Findings in Diagnosis of Gastrointestinal Metaplasia in Patients Referred to the Clinica Colombia for Upper Endoscopies,*" focuses on the search for the relation between endoscopic findings leading to suspicion of intestinal metaplasia and to histological confirmation. This is an analytical observational study in which a correlation close to 70% is found. This result matches perfectly with those found in the literature, although it should be mentioning beforehand that there are very few published studies on this, about which I will comment and relate this value to some issues that explain these findings.

In the first place, conventional white light endoscopy cannot accurately diagnose pre-neoplastic gastric conditions. One of the most important relevant studies is that of Atkins and Benedict in which they concluded that the correlation between endoscopy and histology was poor (4). Even today it is still clear within the studies of correlation that only antral nodularity seems to be an endoscopic sign with a high positive predictive value (over 90%) for Helicobacter pylori infection. One of the most relevant subsequent studies on the correlation of endoscopic findings and histology, because of its prospective nature, was published in the Hepatogastroenterology 1999. It evaluated the reliability of corroborating endoscopic findings for intestinal metaplasia with histology. It is a prospective study in which 87 patients were subjected to endoscopic examination as part of executive checkups. Patients whose endoscopic characteristics showed whitish plaques, patches or homogeneous discoloration on the gastric mucosa were diagnosed as having intestinal metaplasia and assigned to group A. Patients with none of these endoscopic findings were assigned to group B. Biopsies were taken from regions suspected of metaplasia and from normal appearing mucosa for future histologic correlation. In group A there were 8 patients with whitish plaques, 29 with whitish patches and 8 with a homogeneous whitish discoloration. In group B, there were 42 patients with no endoscopic characteristic of IM. After correlating endoscopic findings with histological examinations, 30 patients in group A and 10 patients in group B were histologically confirmed to have intestinal metaplasia. These values showed 75% sensitivity, 68.1% specificity, a 66.7% positive predictive value, a 76.2% negative predictive value and a 71.3% endoscopic diagnostic precision. The conclusion was that the established endoscopic criteria correlated in three quarters of the patients with IM during the routine endoscopic exam. The correlation percentage was 66% (5), similar to the findings of the Colombian study shown here. The 66.7% positive predictive value for endoscopic findings is also very similar to the 71% found in this study.

Intestinal metaplasia may be suspected when an endoscopy finds thin whitish deposits in plaques (6). Nevertheless, the value of this finding for diagnosis of intestinal metaplasia, contrary of what we believe, remains undetermined. This leads to the importance of studies such

as this one that attempt to give an answer to this worldwide concern.

Delving into these matching values, which we all would expect to match greater, various authors suggest that the diagnostic performance of endoscopy in identifying metaplasia may be improved using tinctures. Several studies have been demonstrated that methylene blue, indigo carmine, and acetic acid in conventional chromoendoscopy can be useful for determining these lesions. Methylene blue has shown correlations up to 89% (7). The literature shows that chromoendoscopy with magnification and narrowband imaging (NBI), with or without magnification, improve diagnostic performance for pre-neoplastic conditions.

Chromoendoscopy, particularly with magnification, helps identify pre-cancerous lesions, however, this technique requires extensive experience, prolongs the time of study, adds to work load and requires more patience from the patient. For this reason it is not systematically recommended, but should be reserved for centers with a great deal of experience with this technique.

Narrowband imaging (NBI) techniques show good sensitivity for diagnoses of gastric lesions however there is no agreement about which NBI patterns are associated with pre-cancerous lesions. The various classifications lack external validation, even though several studies conclude that NBI increases better diagnostic acuity than the conventional white light endoscopy for detecting premalignant gastric lesions (8). This suggests that rather than looking for pearly plaques that suggest metaplasia other findings might be used which could be supported by using special or electronic tinctures to try and improve the diagnosis of these lesions.

In addition, in the article's discussion section one of the author's worries is that nearly 49% of pathology reports did not include the type of metaplasia (non-specific metaplasia). I was surprised to find that the literature shows no general consensus that defines whether it is necessary or not to report the type of metaplasia for prognosis and monitoring purposes. Since the literature does not specify the relative frequency when conventional techniques of hematoxylin-eosin cannot classify metaplasia, I think the authors can relax a little regarding this point. The fact that hematoxylin-eosin cannot always classify metaplasia is the reason why "non-specific metaplasia" is frequently reported, and hence the reason why some authors recommend use of additional methods such as immunohistochemistry to provide adequate characterization of a lesion. Let us remember that traditionally the types of intestinal metaplasia suggested as a real risk factor for developing gastric cancer are types IIB and III.

Colonic metaplasia that primarily secretes sulfomucin has been associated with intestinal type gastric cancer and therefore has been considered to be the true pre-neoplastic lesion (9). These observations have yet to be confirmed; hence currents have developed that assert that sub-typing intestinal metaplasia is not necessarily recommended in routine clinical practice (10). Although current classification of intestinal type metaplasia should not generate larger issues, in the pathologist's daily practice it is a real problem because of the coexistence of different phenotypes in a single sample and the distortion of finer cytological details during the sample taking or during the procedure.

I would like to make an additional educational comment to take into consideration arguments related to suspicion of multifocal intestinal metaplasia when taking gastric biopsies. The distributions in the stomach of gastric atrophy and intestinal metaplasia frequently vary. For this reason a minimum of four biopsies from two different topographic areas is suggested. Ideally they should be taken from the greater curvature and lesser curvature of the antrum and gastric body. In addition biopsies should be taken from suspicious areas. It is recommended that to identify lesions suspected of metaplasia, a biopsy should be performed and a sample taken from the suspect area. These biopsies will be necessary if the metaplasia is multifocal and will especially impact surveillance. In addition, some authors recommend biopsies from the incisura angularis. This is the recommendation of the Sydney System for calibration of gastritis which argues that this location is an area where early transformation of atrophy into metaplasia can be detected. Nevertheless, adding these biopsies to the incisura is uncertain and is still not adequately established (11).

With these biopsy sampling recommendations, and given the importance of atrophy and multifocal metaplasia in the early detection of gastric cancer which allows for better survival, endoscopic surveillance should be offered to all patients with extensive atrophy and intestinal metaplasia in the antrum and gastric body. Ideally follow-up examinations should take place every three years following diagnosis. Nevertheless, there is not enough evidence for patients with atrophy and mild to moderate metaplasia confined only to the antrum and non-corpus antrum to recommend surveillance periods (Evidence level 4, grade D recommendation). These surveillance types are based on the progression rates of precancerous lesions for atrophic gastritis (0 to 1.8% per year) and intestinal metaplasia (0 to 10% per year).

Two extensive forms of intestinal metaplasia have been identified. Some have called the areas where the metaplasia is found on the lesser curvature, from the cardiac to the pylorus, "transition areas," whereas "diffuse distribution" is defined as extensive replacement of the gastric mucosa by intestinal type mucosa. These two topographic patterns have increased risks of gastric cancer.

It is possible to conclude that efficient surveillance and early detection of atrophy and intestinal metaplasia are crucial for prevention of gastric cancer. When we perform routine digestive endoscopy here in our country with such high gastric cancer incidence, we should ask ourselves if we are actively looking for indications of precancerous lesions other than the classical whitish pearly plaques. We should ask ourselves if we are also taking adequate samples to improve our diagnostic performance at identifying these lesions. Although it is possible that other findings that have yet to be determined may indicate the presence of metaplasia, it is clear that they will not be easily identified with conventional light endoscopy. Some of the answers may be found by using complementary techniques that will help us improve diagnostic performance and describe new findings.

REFERENCES

1. Rubiano Jaime, Velásquez Mauricio. Atrofia, metaplasia y cáncer gástrico: ¿dónde está la evidencia? Rev Colomb Cir 2007; 22(1).
2. Toyokawa T, Suwaki K, Miyake Y, et al. Eradication of *Helicobacter pylori* infection improved gastric mucosal atrophy and prevented progression of intestinal metaplasia, especially in the elderly population: a long-term prospective cohort study. J Gastroenterol Hepatol 2010; 25: 544-547.
3. M Dinis-Ribeiro, M Areia y cols. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy 2012; 44(1): 74-94.
4. Atkins L, Benedict EB. Correlation of gross gastroscopic findings with gastroscopic biopsy in gastritis. N Engl J Med 1956; 254: 641-644.
5. Rugge M, Cassaro M, Pennelli G, et al. Atrophic gastritis: pathology and endoscopy in the reversibility assessment. Gut. 2003; 52: 1387-1388.
6. Stathopoulos G, Goldberg RD, Blackstone MO. Endoscopic diagnosis of intestinal metaplasia. Gastrointest Endosc 1990; 36: 544-545.
7. Tatsuta, y cols. Chromoendoscopic observation on extension and development of fundal gastritis and intestinal metaplasia. Gastroenterol 1998; 45: 2234-2237.
8. Capelle LG, y cols. Narrow band imaging for the detection of gastric intestinal metaplasia and displasia during surveillance endoscopy. Dig Dis Sci 2010; 55(12): 3442.
9. Rokkas T, Fillipe MI. Detection of an increased incidence of early gastric cancer in patients with intestinal metaplasia type III who are closely followed up. Gut 1991; 32: 1110-1113.
10. Conchillo JM, Houben G, de Bruïne A, et al. Is type III intestinal metaplasia an obligatory precancerous lesion in intestinal-type gastric carcinoma? Eur J Cancer Prev 2001; 10: 307-312.
11. Lin BR, Shun CT, Wang TH, Lin JT. Endoscopic diagnosis of intestinal metaplasia of stomach-accuracy judge by histology. Hepatogastroenterology 1999; 46(25): 162-6.