Review Article

Atrophic gastritis and pre-malignant gastric lesions

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Abstract: Atrophic gastritis and intestinal metaplasia are considered to be precancerous conditions as they constitute the background in which dysplasia and intestinal-type gastric adenocarcinoma may develop. The development of the intestinal-type gastric adenocarcinoma represents the end step of an inflammation-metaplasia-dysplasia-carcinoma sequence, called the Correa cascade of multistep gastric carcinogenesis. Atrophic gastritis is associated also with type 1 gastric carcinoid whose major pathogenetic factor is hypergastrinemia. Gastrin acts as a growth factor for enterochromaffin-like cells, which in atrophic gastritis are chronically induced to proliferate, and, through a multistep process passing from hyperplasia to dysplasia, carcinoid may develop. Atrophic gastritis is a chronic disorder occurring in up to 8% of the general population. The positivity of autoantibodies against parietal cells and/or intrinsic factor, the compresence of autoimmune diseases as thyroid autoimmune disease or type 1 diabetes are frequently observed. A frequent clinical presentation of atrophic gastritis is pernicious anemia arising from vitamin B12 malabsorption as a consequence of intrinsic factor deficiency. Also iron deficiency anemia may be associated with atrophic gastritis due to iron malabsorption as a consequence of reduced gastric acid secretion together with normal or low cobalamin levels. Pernicious anemia, the possible end-stage of atrophic gastritis, is considered an autoimmune disorder. To date, there are no clear universally accepted criteria to define autoimmune gastritis and to distinguish this clinical entity from chronic *Helicobacter pylori* (*H. pylori*)-driven atrophic gastritis. In the last years, many data emerged from several studies on prevalence of atrophic gastritis and intestinal metaplasia, risk of progression of these conditions to gastric neoplasms, clinical features and detection of these precancerous changes in the gastric mucosa. The purpose of this review was to focus on these issues.

Keywords: Atrophic gastritis; pernicious anemia; intestinal metaplasia; gastric cancer; type 1-gastric carcinoids

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Atrophic gastritis: a precancerous condition

Atrophic gastritis is an inflammatory condition characterized by the loss of gastric glandular structures which are replaced by connective tissue (non-metaplastic atrophy) or by glandular structures inappropriate for location (metaplastic atrophy) (1). Gastric mucosal atrophy and intestinal metaplasia confer a high risk for the development of gastric cancer as they constitute the background in which dysplasia and intestinal-type gastric adenocarcinoma may develop (2,3). For this reason, atrophic gastritis and intestinal metaplasia are considered to be precancerous conditions.

In many cases, the development of the intestinal-type gastric adenocarcinoma represents the end step of an inflammation-metaplasia-dysplasia-carcinoma sequence, also called the Correa cascade of multistep gastric carcinogenesis. According to this cascade, gastric cancer develops as a consequence of a gradual progression from normal gastric mucosa through chronic *Helicobacter pylori* (*H. pylori*)-related non-atrophic gastritis, atrophic gastritis, and intestinal metaplasia, to dysplasia and carcinoma (4,5). Longitudinal studies have confirmed this model (6,7).

Different phenotypes of atrophic gastritis may develop due to different environmental exposure and genetic profiles. The intra-gastric distribution of premalignant

changes of the gastric mucosa is one determinant of gastric cancer risk: cases of oxyntic gland atrophy and/or intestinal metaplasia distributed in a multifocal pattern including the lesser curvature of the corpus and fundus, are called multifocal atrophic gastritis, and this phenotype, described as "extensive", has been associated with a higher risk of gastric cancer. Similarly, the concept of 'gastritis of the carcinoma phenotype' proposes that the corpus-predominant gastritis increases the risk of gastric cancer, likely due to changes of the intra-gastric milieu as increased pH, reduced ascorbic acid (AA) and scavenging of nitrites and other potential carcinogenic substances (8-10).

Intestinal metaplasia may be classified as "complete" or "incomplete", where complete intestinal metaplasia displays goblet and absorptive cells, decreased expression of certain gastric mucins as MUC1, MUC5AC, and MUC6, but expression of the intestinal mucin MUC2. In contrast, incomplete intestinal metaplasia displays goblet and columnar non-absorptive cells co-expressing gastric and intestinal mucins (11-13). Some studies indicate a positive correlation between the extent of intestinal metaplasia and the degree of incomplete intestinal metaplasia, but in routine diagnostics, subtyping of intestinal metaplasia is not widespread.

More recently, a third pattern of intestinal metaplasia has been described, known as the spasmolytic polypeptide-expressing metaplasia (SPEM), which is characterized by the expression of the TFF2 spasmolytic polypeptide, associated with oxyntic atrophy. This pattern of intestinal metaplasia, observed in the gastric body, has been reported to be strongly associated with *H. pylori* infection and gastric cancer, and may possibly represent another pathway to gastric neoplasia (14). A very recent study conducted in Taiwan showed that genomic single nucleotide polymorphisms (ITGA5-1160/ITGB1-1949/ITGB1 + 31804 as T/A/C carriers and COX-2-1195/IL-10-592 as G-carrier/AA) in the offspring of gastric cancer patients predispose to SPEM after *H. pylori* infection, and may serve as marker to identify high-risk subjects for *H. pylori* eradication (15).

Gastric dysplasia represents the penultimate stage of the sequence of gastric carcinogenesis. This lesion is histologically defined as unequivocal neoplastic epithelium without evidence of tissue invasion (16), which is characterized by cellular atypia reflective of abnormal differentiation and disorganized glandular architecture. Gastric dysplasia thus, is to be considered a direct neoplastic precancerous lesion. The Padova, Vienna, and WHO classifications are proposals to standardize the terminology for the morphological spectrum of gastric dysplastic lesions (17-20).

Epidemiological data suggest that atrophic gastritis is associated not only with intestinal-type gastric cancer, but also with type 1 gastric carcinoid. The pathophysiological mechanisms which lead to the development of these gastric tumors are profoundly different. As mentioned above, gastric cancer develops as the final result of a multistep process initiating from *H. pylori*-related gastritis to atrophic gastritis, intestinal metaplasia and dysplasia (4). In contrast, type 1 gastric carcinoids are gastrin-dependent tumors. These tumors are well-differentiated with low proliferative index and a generally benign behavior, and constitute up to 80% of all gastric carcinoids (21). A major pathogenetic factor for type 1 gastric carcinoids is hypergastrinemia due to atrophic gastritis. Gastrin acts as a growth factor for enterochromaffin-like cells, which in atrophic gastritis are chronically induced to proliferate, and, through a multistep process passing from hyperplasia to dysplasia, carcinoid may develop (21-23).

Several events occur in the gastric mucosa before the development of gastric cancer or type 1 gastric carcinoid, and these events may take several years. Thus, the knowledge of atrophic gastritis prevalence in different clinical settings, its clinical features and possible risk factors associated with the progression of this condition to gastric neoplasms are important issues.

Atrophic gastritis: epidemiology and clinical features

Atrophic gastritis is a chronic disorder occurring in up to 8% of the general population, mainly characterized by atrophy of the oxyntic glands with consequent lack of gastric acid and, in a late stage, lack of intrinsic factor production. Often, the positivity of autoantibodies against parietal cells and/or intrinsic factor, the compresence of autoimmune diseases as thyroid autoimmune disease or type 1 diabetes are observed (24-27). In a study conducted in 2008 (27), of the 319 atrophic gastritis patients investigated, 169 (53%) had an associated thyroid disorder, and 89 (52.7%) of these were unaware of it. The thyroid disease was autoimmune in 128 patients (75.7%) and non-autoimmune in 41 patients. Logistic regression showed that risk factors for having autoimmune thyroid disease in atrophic gastritis patients were female gender (odds ratio 5.6), presence of parietal cell antibodies (odds ratio 2.5), and presence of metaplastic

atrophy (odds ratio 2.2). These data show that autoimmune thyroid disease and atrophic gastritis occur in a closely linked fashion, and they suggest that atrophic gastritis patients should be investigated for an occult autoimmune thyroid disease, in particular women and those with positive parietal cell antibodies (27).

A frequent clinical presentation of atrophic gastritis is pernicious anemia, a megaloblastic anemia arising from vitamin B_{12} malabsorption as a consequence of intrinsic factor deficiency (28,29). Atrophic gastritis may present also with iron deficiency anemia due to iron malabsorption as a consequence of reduced gastric acid secretion together with normal or low cobalamin levels (30,31), and some of these patients may over time develop overt pernicious anemia (32). The reasons for these different clinical presentations of patients with atrophic gastritis harbouring similar gastric alterations virtually leading to vitamin B_{12} deficiency are not known and may have a genetic basis. In a recent study, in which a panel of single nucleotide polymorphisms related to cobalamin absorption was investigated in atrophic gastritis patients with and without pernicious anemia compared to healthy controls, showed that a genetic variant of transcobalamin II, related to lower vitamin B_{12} levels, was more frequent in pernicious anemia patients compared to controls, showing the plausibility of genetic factors determining the possible clinical manifestation of atrophic gastritis (33).

Pernicious anemia, the possible end-stage of atrophic gastritis, is considered an autoimmune disorder (28,29). To date, there are no clear universally accepted criteria to define autoimmune gastritis and to distinguish this clinical entity from chronic *H. pylori*-driven atrophic gastritis. In a previous work it was shown that features which should help to discriminate between autoimmune and not-autoimmune gastritis, as positivity to intrinsic factor and parietal cells antibodies, presence of enterochromaffin-like cells, pernicious anemia and active *H. pylori* infection, were similar in patients with corpus-restricted atrophic gastritis (the classical histological feature of autoimmune gastritis) and those with antral and corporal atrophic gastritis (mainly attributed to *H. pylori* infection), indicating that the specific clinical-histological features associated with autoimmune gastritis are far from being well defined (31).

A recent systematic review evaluated the atrophic gastritis incidence in patients free of atrophic gastritis at moment of inclusion in the study (34). The authors selected 14 follow-up studies in which atrophic gastritis was diagnosed by histology (12 studies) or by serum pepsinogen (two studies). The atrophic gastritis incidence rates ranged from 0 to 10.9% per year, probably explained by the particular clinical settings in which the atrophic gastritis diagnoses were made, including patients with reflux esophagitis and those successfully treated for *H. pylori* infection with lowest incidence rates (0%) (35,36) and patients who underwent vagotomy due to peptic ulcer with highest incidence rate (37). In a meta-analysis, the rate ratios comparing the atrophic gastritis incidence in *H. pylori* positive patients to that in *H. pylori* negative ones ranged from 2.4 to 7.6 with a summary estimate of 5 (95% CI: 3.1-8.3) (34).

In other studies, the prevalence of atrophic gastritis was evaluated by serological screening using surrogate markers of gastric function (pepsinogen I or pepsinogen I/pepsinogen II ratio) or by gastroscopy/histology. In many cases, the serological and histological screenings were both made in a general population. Serological studies reported atrophic gastritis prevalence rates between 3% and 7%, which were lower than those reported by histological ones (38-47). Higher rates of atrophic gastritis prevalence found in the Asian countries may be justified by the higher risk of gastric cancer in these areas are and the different definition of atrophic gastritis diagnosis between Western and Asian countries. In studies reporting from Asian countries, atrophic gastritis diagnosis included all atrophic lesions irrespective of the atrophy localization in the gastric mucosa (antrum and/or corpus); in the vast majority of the studies conducted in Western countries, atrophic gastritis diagnosis included only patients with a corpus atrophic involvement such as corpus-atrophic gastritis or a multifocal atrophic gastritis.

A very recent serological study on 5,284 participants in Sweden (48) documented an increase in the prevalence of atrophic gastritis among adults aged 35-44 years from 22 to 64/1,000 between 1990 and 2009, but a decrease prevalence of atrophic gastritis in participants 55-64 years old from 124 to 49/1,000 in the same observation period. The stabilizing seroprevalence of *H. pylori* and increasing prevalence of overweight and obesity might contribute to this unexpected trend; however, studies are needed to determine whether these changes have affected the incidence of gastric cancer (48).

Atrophic gastritis and risk of gastric neoplasms

Gastric cancer is still the fourth most common cancer worldwide and the second cause of cancer-related death (49). A varying progression rate of atrophic gastritis to gastric cancer up to 2% per year has been reported at follow-up

Table 1 The incidence rates of gastric cancer and type 1 gastric carcinoid were not different in atrophic gastritis patients at long-term follow-up (64)

Gastric neoplasms	Annual incidence rate person-year (%)	95% confidence interval
All	1.36	0.85-2.06
Gastric cancer	0.25	0.067-0.63
Dysplasia	0.43	0.17-0.89
Type 1 gastric carcinoids	0.68*	0.34-1.21

Data from Lahner E, *et al*. Scand J Gastroenterol 2015;3:1-100. *, compared to gastric cancer: P=0.07.

periods ranging from 1 to 16 years (50-52). A recent systematic review showed in atrophic gastritis patients with pernicious anemia a pooled gastric cancer incidence-rate of 0.3% person-year and an estimated 7-fold relative risk of gastric cancer (53).

In patients with atrophic gastritis also type 1 gastric carcinoids may arise. Data on long-term incidence of type 1 gastric carcinoids are scanty (54-56). A recent cohort study reported an annual incidence rate for type 1 gastric carcinoid of 0.4% (57), while an older study reported an annual incidence of 2%, observing eight new cases of type 1 gastric carcinoids in 416 patient-year (55). In the above cited study, pernicious anemia was present in almost 50% of patients with type 1 gastric carcinoids (57), while previous studies included exclusively patients with this condition (55,56,58-60). In patients with atrophic gastritis, the need and cost-effectiveness of regular endoscopic follow-up for gastric cancer surveillance is not definitely established. Recent European guidelines recommend a scheduled surveillance for gastric cancer for those patients who have extensive—i.e., both antrum and gastric body—atrophic gastritis or intestinal metaplasia (61). However these guidelines are not addressed to patients with pernicious anemia, as corpus-restricted atrophic gastritis with antrum-spared, typically present in pernicious anemia patients, is not considered to be part of the precancerous cascade described by Correa (4). According to the data reported, different clinical management of atrophic gastritis patients with or without pernicious anemia does not seem to be justified, raising questions whether these recommendations should include also pernicious anemia patients.

With regard to surveillance for type 1 gastric carcinoids, indications are even more uncertain. A recent study on endoscopic management of these tumours, reported that for atrophic gastritis patients without recurring type 1 gastric carcinoids, endoscopic controls might be planned yearly in the early follow-up, but can probably become less intensive with endoscopic controls every 4 years according to atrophic gastritis screening for gastric cancer risk (62). To better evaluate the value of surveillance in atrophic gastritis patients and establish follow-up frequencies, more precise data on the occurrence of gastric neoplastic lesions, preferably obtained in large prospective studies with adequate follow-up, are needed (63).

The combined risk of gastric cancer and carcinoids together has been investigated many years ago limited to pernicious anemia patients (55,56). A recent study (64) investigated in a prospective cohort of patients with atrophic gastritis the occurrence of gastric cancer and carcinoids at long-term follow-up from 4 years upwards. In this study a total of 200 atrophic gastritis patients from a prospective cohort (67% females, median age 55 years) with a follow-up of 7.5 (range, 4-23.4) years were included. Follow-up gastroscopies at 4-years intervals were performed. The results of this study showed that, overall, 22 gastric neoplastic lesions were detected (crude incidence 11%). Gastric cancer was diagnosed in four patients at a median follow-up of 7.2 years (crude incidence 2%). Eleven type 1-gastric carcinoids were detected at a median follow-up of 5.1 years (crude incidence of 5.5%). In seven patients, six low-grade and one high-grade dysplasia were found. As shown in *Table 1*, the annual incidence rates person-year were 0.25%, 0.43%, and 0.68% for gastric cancer, dysplasia, and type 1-gastric carcinoids, respectively. From this study emerged that in atrophic gastritis patients at long-term follow-up an annual incidence rate of 1.36% person-year for gastric neoplastic lesions and that the incidence rates of gastric cancer and type 1 gastric carcinoid were not different (P=0.07), indicating that atrophic gastritis patients are similarly exposed to both risks (64). According to Globocan 2012, the annual incidence rate for gastric cancer in the general Italian population is estimated to be 0.004% (65). This study thus provides further evidence confirming the increased risk for gastric cancer in atrophic gastritis.

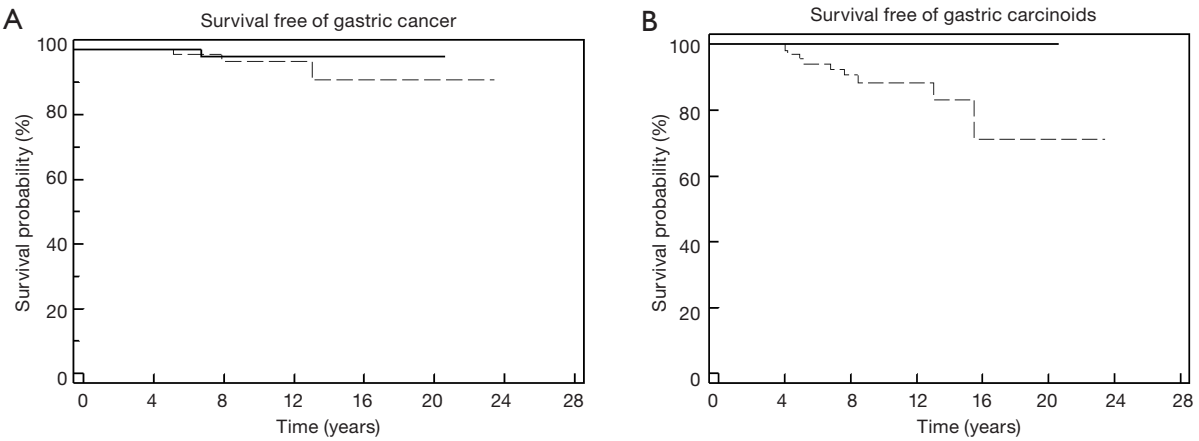

Figure 1 Kaplan-Meier survival curves showing the survival time in years free of gastric cancer (A) and free of gastric carcinoids (B) with respect to pernicious anemia. (A) Solid line = absence of pernicious anemia; broken line = presence of pernicious anemia, comparison of survival curves (Logrank test): P=0.3551; (B) Solid line = absence of pernicious anemia; broken line = presence of pernicious anemia, comparison of survival curves (Logrank test): P=0.0023.

As shown in *Figure 1*, the presence of pernicious anemia is associated with gastric carcinoids but not with gastric cancer, as survival free of carcinoids is significantly shorter in patients with pernicious anemia.

The patients' features associated with gastric cancer and type 1 gastric carcinoids are different, keeping in step with the different pathogenetic mechanisms of these two type of tumors (4,21). The occurrence of type 1 gastric carcinoids is mainly associated with features of autoimmune gastritis as pernicious anemia and positivity to gastric autoantibodies. Gastric cancer, instead, is associated with the presence of *H. pylori* in the corporal mucosa (HR 8) (64) keeping in step with the concept of corpus-predominant gastritis as observed by Uemura more than ten years ago that *H. pylori* positive patients and those with severe gastric atrophy, corpus-predominant gastritis or intestinal metaplasia are at increased risk for gastric cancer (9). *Figure 1* shows the Kaplan curves of gastric cancer and carcinoids with respect to pernicious anemia: The presence of pernicious anemia is associated with gastric carcinoids but not with gastric cancer, as survival free of carcinoids is significantly shorter in patients with pernicious anemia.

Atrophic patients are exposed to a double risk of gastric neoplastic lesions, gastric cancer and type 1 gastric carcinoids. In a retrospective case-series (66), the occurrence of gastric cancer in patients with type 1 gastric carcinoids was described in 23% (4 out of 17) of patients with type 1 gastric carcinoids over a median follow-up period of 6 years. Three cases were intestinal-type adenocarcinomas and one a signet-ring cells diffuse gastric cancer, localized in three cases in the antrum. Thus, it seems to be worthwhile to monitor type 1 gastric carcinoids patients by a long-term surveillance programme, including an accurate bioptic sampling of antral mucosa. The effects of long-standing hypergastrinemia may be a possible explanation why patients with type 1 gastric carcinoids might develop more frequently gastric cancer. Hypergastrinemia has been proposed in many models of gastric carcinogenesis and seems to be a common causative factor in otherwise different circumstances; in all species where long-term hypergastrinemia has been induced, an increased risk of gastric malignancy, with adenocarcinoma phenotype and even the signet-ring cells phenotype, was observed (67,68). Moreover, the long-term conservative management of type 1 gastric carcinoids exposes these patients to a higher risk of gastric cancer. This risk is basically present in atrophic gastritis, due to the pathophysiological changes related to gastric body atrophy, such as increased pH, reduced AA and scavenging of nitrites and other potential carcinogenic substances (69).

It has become apparent that besides *H. pylori*, other bacteria may be involved in gastric carcinogenesis; it has been shown that the gastric cancer microbiota was dominated by species of the genera *Streptococcus*, *Lactobacillus*, *Veillonella* and *Prevotella*, albeit the roles of these species in the development of gastric cancer needs to be determined (70). *Figure 2* gives a schematic overview of changes of the intragastric milieu possibly involved in the higher risk of gastric neoplasms in

Figure 2 Schematic overview of changes of the intragastric milieu possibly involved in the higher risk of gastric neoplasms in patients with atrophic gastritis. Pathophysiological changes related to mucosal atrophy of corporal mucosa: (I) reduced acid secretion (HCl); (II) reduced AA and other antioxidants; (III) changes in the gastric microbiota: presence of other bacteria besides Helicobacter pylori having a possible role in gastric carcinogenesis. AA, ascorbic acid.

patients with atrophic gastritis.

Detection of atrophic gastritis and premalignant changes

Although the gastric cancer incidence has declined over the past decades, especially in Western countries, the mortality rate due to gastric cancer remains high (71). Detection and surveillance of patients with premalignant conditions, as atrophic gastritis and intestinal metaplasia, could potentially lead to detection and treatment of advanced lesions—i.e., dysplastic lesions and gastric cancer—in an early stage (72-74). In patients with premalignant conditions, the risk of developing gastric cancer may be further stratified by the location, severity, and extent of gastric atrophy and/or metaplasia (75,76).

Several histological classifications have been developed for atrophic gastritis and preneoplastic changes. To date, in clinical practice and in research, the updated Sydney System is mainly used. This system combines topographic, morphological, and etiological information to standardize histological reporting (77). More recently, the systems known as OLGA (operative link for gastritis assessment), and OLGIM (operative link on gastric intestinal metaplasia) assessment have been proposed for staging of gastritis (78). Unfortunately, classifications are still difficult to use in clinical practice, and often present the disadvantage of important inter- and intra-observer variation (79).

As mandatory conditions to correctly adopt premalignant gastric lesions as reliable indicators for gastric cancer development, a standardized biopsy sampling protocol and an uniform, reproducible histological grading system need to be applied in clinical practice (61). A recent nationwide survey investigated in a community-based endoscopic setting what really happens in clinical practice with regard to the detection of gastric atrophy and intestinal metaplasia in dyspeptic patients (80). In detail, a nationwide survey was conducted on 979 consecutive patients (50-65 years old) with dyspeptic symptoms, who were examined at 24 gastrointestinal endoscopy units throughout Italy. Clinical information was collected from questionnaires; a standard bioptic mapping was performed in each unit, biopsies from each patient were analyzed by histopathology performed according to daily clinical practice in each local pathology centre. The results showed that separate descriptions of antral and corporal biopsies were included in 679 pathology reports (69%), whereas the standardized Sydney system was applied in 324 reports (33%). Gastric atrophy without intestinal metaplasia and gastric atrophy with intestinal metaplasia were detected in 322 (33%) patients. The full adherence to Sydney system significantly increased the probability of detecting gastric atrophy with intestinal metaplasia (OR =9.6; 95% CI: 5.5-16.7), gastric atrophy without intestinal metaplasia (OR =1.92; 95% CI: 1.07-3.44), and either of the conditions (OR =6.67; 95% CI: 4.36-10.19). Thus, according to these findings, in daily routine practice only one third of histology reports were worked out adhering to Sydney system showing that international guidelines are poorly observed in clinical practice (80). This may represent a critical element for surveillance strategies for gastric cancer.

Conclusions

Atrophic gastritis and intestinal metaplasia are premalignant changes, which, in a large part of patients fortunately will never progress to intestinal-type adenocarcinoma or type 1 gastric carcinoid. Many efforts have been done till now to obtain knowledge about these conditions and to optimize

the management and surveillance of patients harbouring atrophic gastritis and/or intestinal metaplasia. Recently, it has been reported that nanoarray analysis is able to detect precancerous gastric lesions and gastric cancer through exhaled breath, and that possibly it could provide the missing non-invasive screening tool for gastric cancer and related precancerous lesions as well as for surveillance of the latter (81). While awaiting the validation of these or other innovative tools, important issues need to be better addressed, as the inclusion of patients with autoimmune gastritis and pernicious anemia amongst patients at higher risk for gastric cancer and carcinoids and the optimal time interval and cost-effectiveness of endoscopic-histological follow-up in patients with atrophic gastritis and intestinal metaplasia.

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Footnote

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