# FROM PREMALIGNANT LESIONS TO EARLY GASTRIC CANCER

## WHAT IS CLINICALLY RELEVANT?

ed, Tamara Matysiak-Budnik

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# SUMMARY

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MARCUS AURELIUS (IX,5)

# Foreword

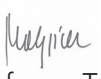
Dear Reader,

It is our great pleasure to introduce this book whose main objective is to present the current knowledge on gastric premalignant lesions and early gastric cancer, and the clinical approaches for patients with these lesions. Gastric cancer is a deadly neoplasm with dismal prognosis if diagnosed at an advanced stage, and the best way to reduce the mortality from this cancer is to diagnose it at an early, curable stage, allowing for an effective and conservative, endoscopic treatment. This implies our capacity to identify the patients at risk of gastric cancer, i.e. harboring gastric precancerous lesions, to follow them up correctly, and to be able to detect and treat early gastric cancer. Our knowledge on pathogenesis and evolution of gastric precancerous lesions, like atrophic gastritis, gastric intestinal metaplasia and dysplasia, has improved considerably in the last decades. At the same time, great progress has been made in the field of endoscopy, leading to the introduction of novel and more efficient techniques for the detection and even possible treatment of gastric lesions.



Our objective is to bring all this knowledge to our Reader, by presenting it in a very clear and practical way, thus allowing the incorporation of this knowledge into daily clinical practice. This book covers different aspects of gastric cancer and gastric precancerous lesions, including the latest data on epidemiology and screening of gastric cancer, histological aspects and pitfalls in histological diagnosis of gastric precancerous lesions, an update on the role of *Helicobacter pylori* and the place of non-invasive methods in the diagnosis of gastric precancerous lesions, the latest recommendations on the surveillance of patients with these lesions, and the role of endoscopy and new endoscopic techniques in the detection of gastric intestinal metaplasia and treatment of early gastric cancer. The authors of this book are well recognized world experts in this field, who put effort into addressing all these topics in a simple and didactic way, underligning the practical information that is important for Clinicians.

We do hope that this book will bring useful information and become a practical guide for our Colleagues.



Professor Tamara Matysiak-Budnik

# Epidemiology of gastric cancer: New trends of increasing incidence?

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## CURRENT GLOBAL BURDEN

With over 1 million new cases and close to 800,000 deaths in 2018, gastric cancer is the fifth most frequently diagnosed cancer and the third-leading cause of cancer death worldwide [1,2]. From a global perspective, it therefore remains an important cause of cancer-related incidence and mortality. Incidence rates vary substantially across countries and world regions, ranging from 22 per 100,000 person-years in Eastern Asia to less than 5 per 100,000 in Africa, North America and Northern Europe. Countries with the highest incidence rates of gastric cancer include the Republic of Korea, Mongolia and Japan (*figure 1*). Patterns in mortality are closely aligned with those of incidence, given the frequently late detection of the tumour and high cancer-related fatality (*figure 2*). Yet, while gastric cancer ranks among the top causes of cancer-related death in many transitioning countries, a proportionally lower share of deaths from the disease can be observed in highly developed countries. Incidence rates are generally two-fold higher in men relative to women (*figure 3*) and have been observed to disproportionally affect certain population subgroups, such as persons of lower socioeconomic status, ethnic and indigenous populations and immigrants from high-risk areas [3-5]. For example, gastric cancer incidence and mortality were shown to be elevated in almost all indigenous peoples relative to corresponding non-indigenous populations in the same regions or countries, particularly among Inuit residing in the circumpolar region and among Maori [4]. A comprehensive systematic review and meta-analysis published recently also showed that immigrants from regions with a high incidence of gastric cancer living in regions with low incidence maintain a higher risk of gastric cancer and related mortality [6].

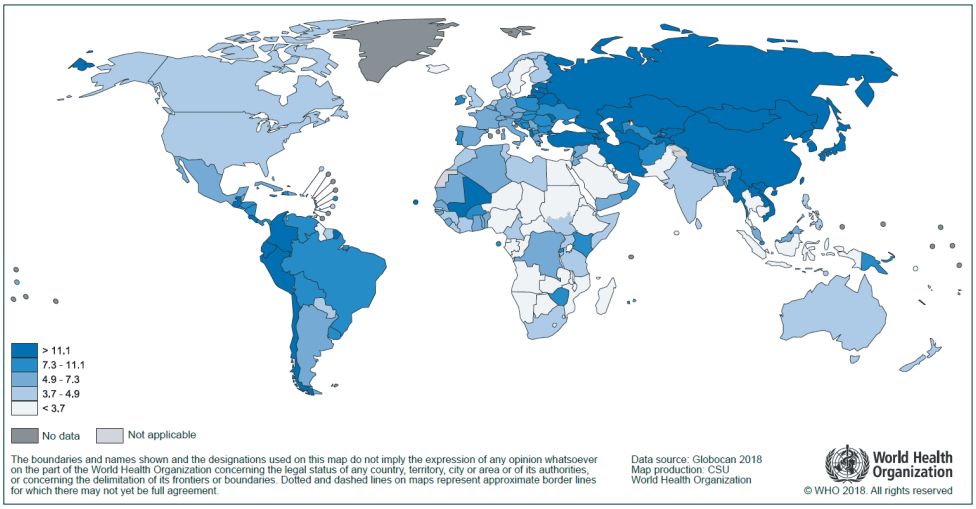


FIGURE 1. Age-standardized incidence rates (World Standard Population) from gastric cancer in 2018, both sexes combined.
Source: GLOBOCAN 2018 (gco.iarc.fr/today)

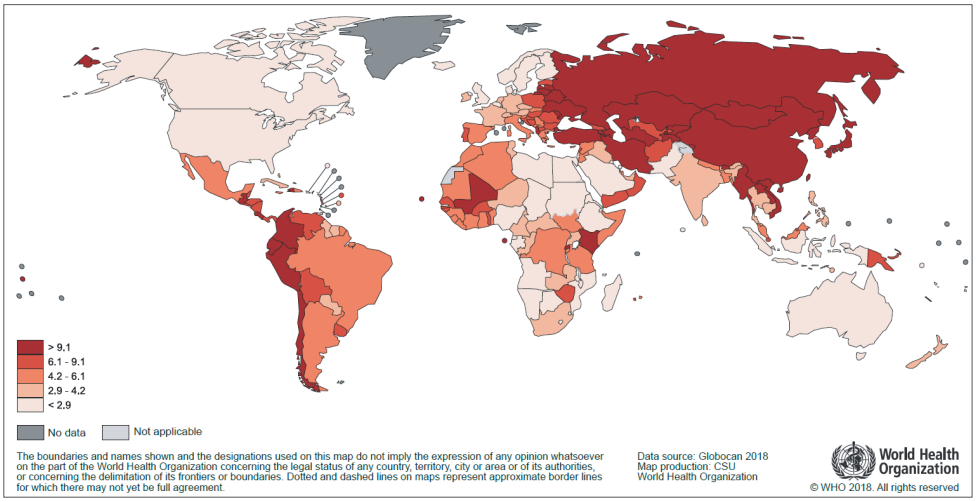


FIGURE 2. Age-standardized mortality rates (World Standard Population) from gastric cancer in 2018, both sexes combined.
Source: GLOBOCAN 2018 (gco.iarc.fr/today)

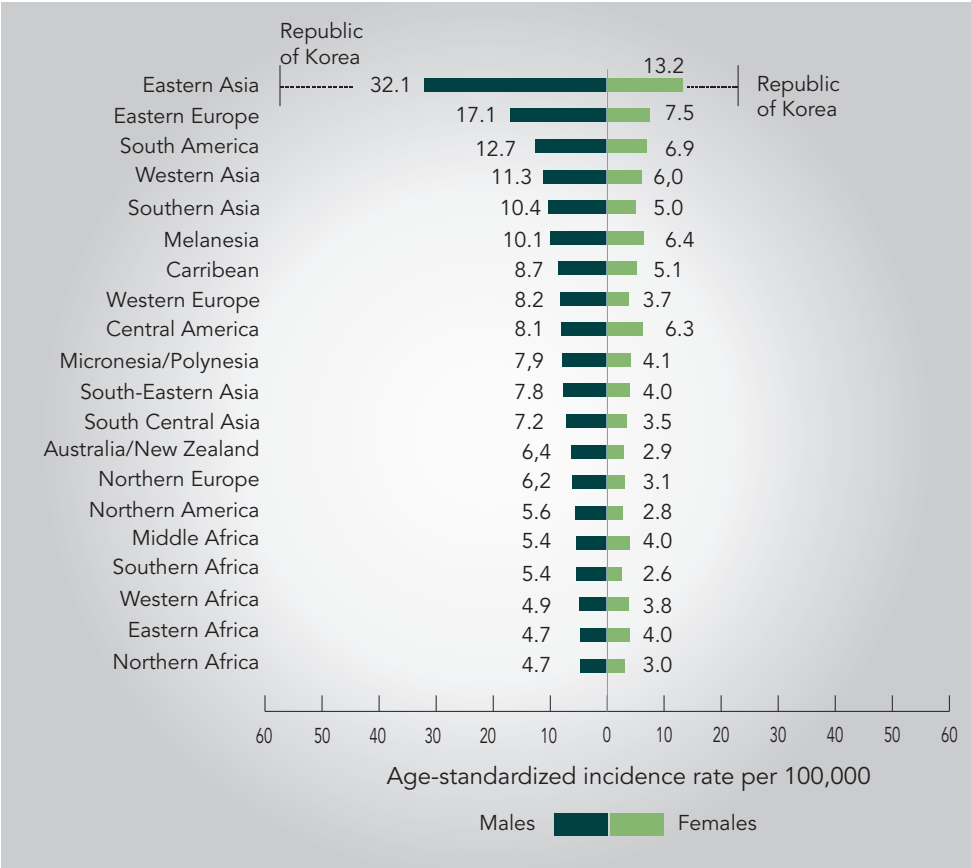


FIGURE 3. Age-standardized incidence rates (World Standard Population) from gastric cancer in 2018 by world region in males and females.
Source: GLOBOCAN, 2018 (gco.iarc.fr/today)

Although often reported as a single entity, gastric cancers can be broadly classified into two major topographical subsites, the cardia and non-cardia. The cardia gastric cancer arises in the area of the stomach adjoining the oesophageal-gastric junction, while non-cardia gastric cancer develops from more distal regions of the stomach, and the two entities differ in terms of aetiology, risk factors and geographical patterns. While cardia gastric cancer is associated with obesity and gastroesophageal reflux disease in Western populations (resembling etiological factors attributed to oesophageal adenocarcinoma), the vast majority of non-cardia gastric cancer cases are associated with *Helicobacter pylori* infection. According to recent estimates for the year 2018, an estimated 18% (or 181,000 cases) of all gastric cancer cases occurred in the cardia and 82% (853,000 cases) occurred in non-cardia regions of the stomach [7]. However, the contributions of non-cardia gastric cancer and cardia gastric cancer to the overall burden from gastric cancer vary greatly across world regions (*figure 4*). Tthe proportion of cardia gastric cancers tends to be highest in highly developed countries and relatively low in most high-risk populations, such as China or Japan, exceptions include a high proportion of cardia gastric cancers in the high-incidence regions of Iran [8-10]. Risks for each subsite also differ across ethnic groups, with, for example, cardia gastric cancer being more common in non-Hispanic whites in the United States (US) than in other ethnic groups [3].



## TRENDS IN INCIDENCE AND MORTALITY

*Figure 5* shows the trends in overall age-standardized gastric cancer incidence and mortality rates in various countries across world regions since the beginning of cancer registration using the data from the International Agency on Cancer's (IARC) Cancer Incidence in Five Continents (CI5) plus Database and the World Health Organization (WHO) Mortality Database [11]. Due to its delayed detection in most countries, mortality and incidence show similar, consistently decreasing trends over time with the exception of a few countries, such as Japan and the Republic of Korea, where the incidence rates have historically been high and have remained largely stable over time, even though mortality has been decreasing. Both countries have a national gastric cancer screening program in place and opportunistic upper endoscopic screening is widely accepted, likely contributing to the observed patterns in incidence and mortality. The decreasing rates of gastric cancer have been attributed to improved socio-economic status, improved sanitation, changes in diet and lifestyle, widespread antibiotic use, and, predominantly, the decreasing prevalence of *Helicobacter pylori* infection [12-14].

Despite the overall decrease in gastric cancer incidence and mortality rates over the last decades, increasing incidence rates of gastric cancer have been observed in

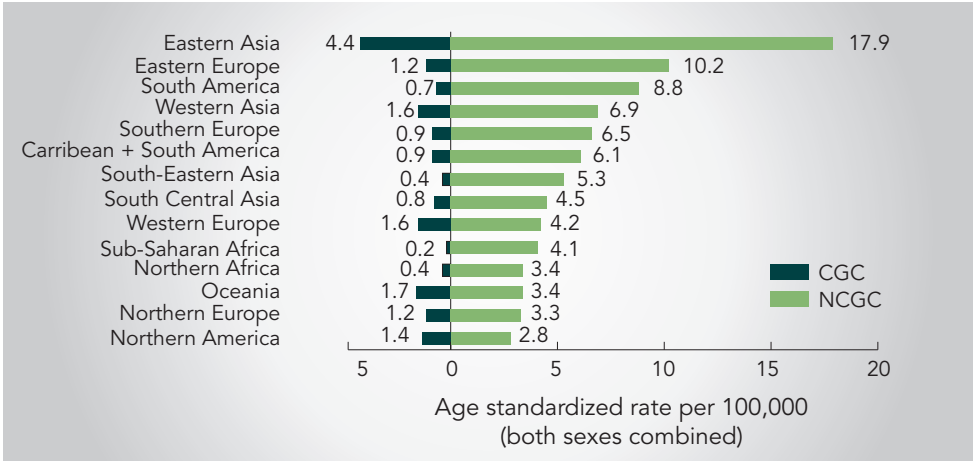


FIGURE 4. Age-standardized incidence rates from cardia (CGC) and non-cardia (NCGC) gastric cancer in 2018 by world region, both sexes combined. 7

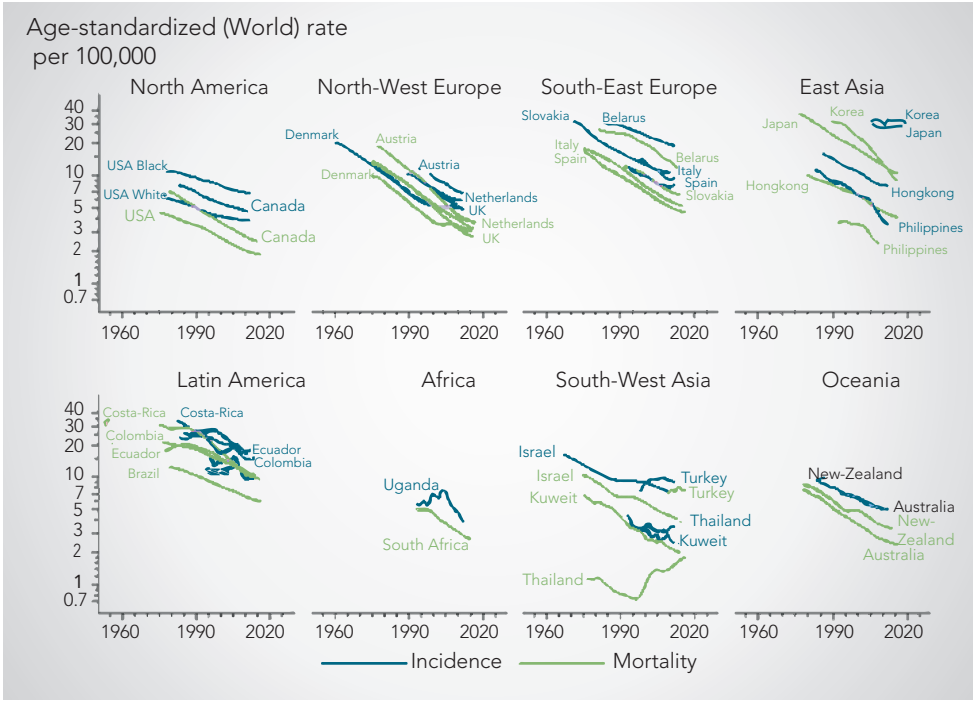


FIGURE 5. Trends in age-standardized incidence and mortality rates (World Standard Population) from gastric cancer in 2018 by country (source: CI5plus and WHO mortality database, reprinted from "*Global Burden of 5 Major Types of Gastrointestnal Cancer*"). 11

sub-populations of several countries. Using the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) from 1977-2006, significantly increasing incidence rates of gastric cancer were reported in US whites aged 25-39 years old (estimated annual percentage change (EAPC)=2.7%)[15]. This observation was largely driven by a significant increase in the incidence rates of gastric corpus cancer among younger and middle-aged whites and non-Hispanic whites (EAPC between 1999 and 2007 = 4.5% in whites and 5.7% for non-Hispanic whites for 25-39 years old, respectively)[16]. More recently, rising incidence patterns among persons below the age of 50 were confirmed using more recent data in the US, contrasted by a significant decrease in incidence in their older counterparts (EAPC for 1995-2013 = 1.3% for age <50 y vs.-2.6% for age >50y, respectively) [17]. Analysing the trends by anatomical subsite in non-Hispanic whites, increased rates for corpus gastric cancer in younger birth cohorts and falling rates in older cohorts were observed (EAPC 4.6% for age<50y vs. -0.5% for age < 50y, respectively). The increases were more pronounced among women than men and largely limited to non-Hispanic whites [17].



The stable or increasing incidence rates of gastric cancer in younger birth cohorts were also observed in several countries outside the US, such as Brazil, Denmark, India and Israel [18]. In Korea, despite the overall, moderate decreasing trends in the incidence of gastric cancer, an increasing trend was reported between 1999 and 2010 especially in women between 40 and 54 years of age [19]. An updated analysis of data between 1999 and 2014 in Korea confirmed the non-decreasing, stable incidence rates of gastric cancer for those who are under 50 years old. The study reported an EAPC of 3.7 % for non-cardia tumours localized to the gastric corpus compared to cardia/fundus (EAPC 1.3%) or antrum (EAPC 1.3%) [20]. Similarly, more recent stable trends in incidence of corpus and pylorus sites have been observed in the Netherlands despite the overall decreasing trend [21]. Together, such trends may lead to a deceleration or a reversal of the overall declining gastric cancer rates in the future.

These increasing trends of corpus-dominant, young age–dominant, female-dominant, so-called "CYF" gastric cancers observed in the US and other countries were assumed to resemble or follow a pattern of oesophageal cancer, which began in highly developed countries [22]. Several hypotheses for changing trends include changing gastric microecology, with disappearance of *Helicobacter pylor*i and auto-immunity, with increasing trend of cancers in the corpus of the stomach where the autoimmune type of gastritis predominates [22,23]. Continued efforts are warranted to investigate whether such changes in trends are observed elsewhere and involve different aetiology.

At the same time, a careful interpretation is required when interpreting trends by cancer subsite given an often large proportion of tumours with unspecified

location. Increasing incidence rates in a known subsite of gastric cancer therefore might not be an accurate reflection of actual increases, with some of the increases being potentially attributable to the increasingly better attribution of the previously unspecified category.

## SURVIVAL AND PROGNOSTIC FACTORS

Although advances in the clinical management of gastric cancer have led to small improvements in outcomes over the past years, five-year survival remains poor, in the range of 20-30% in most countries worldwide [24-26]. Recent analyses of population-based cancer registry data from high-income countries with similar access to health care indicated that while progress has been made, specifically among patients aged below 75, international survival disparities in gastric cancer continue to persist [25]. Patients with gastric cancer are diagnosed at an earlier stage in countries where established screening programs exist compared to the US or other countries where no screening programs are in place (*table 1*). In the Republic of Korea, for example, where gastric cancer incidence is amongst the highest in the world, the implementation of national screening programs using endoscopic and/or radiographic methods has led to an increasing number of cases diagnosed at an early, curable stage and high five-year survival rates of over 76% between 2013-2017 [27].The most important prognostic factor determining survival from gastric cancer is stage at diagnosis, with 5-year net survival of above 60% for early gastric cancer in contrast to approximately 5% for advanced disease [28,29]. Survival from gastric cancer may furthermore depend on the anatomical subsite and histological type. Proximal gastric cancers as well as cancers of the diffuse Lauren type histology [30] have a worse prognosis when compared to distal (non-cardia) and intestinal types [31,32].



## FUTURE BURDEN

According to recent estimates, the number of gastric cancer cases is set out to grow from just over 1 million in 2018 to more than 1.7 million in 2040 as a result of demographic changes, i.e. population aging and growth [2]. Recent country-level analyses showed that the absolute number of new gastric cancer cases is expected to further increase in the next decades in many of the countries included in the study despite the decreasing trend of incidence rates [12]. In addition, while generally decreases or stabilisation of incidence rates were observed in those aged 50 years and above, this was not always the case in the younger age groups. Increases in incidence in those younger than 50 years were predicted in 15 out of 34 countries with both low- and high-incidence, including Belarus, Chile, the Netherlands, Canada and the UK, using the IARC's high-resolution cancer registry data [12].

Table 1. Comparison of gastric cancer stage at diagnosis and 5-year net survival in various countries.

| | USA [1] | | Japan [2] | | Australia [3] | | Netherlands [4] | | Republic of Korea [5] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Years | 2010-2016 | | 2009-2011 | | 2012-2014 | | 2010-2014 | | 2006-2010 | |
| Stage at diagnosis | % of all cases | 5-years NS | % of all cases | 5-years NS | % of all cases | 5-years NS | % of all cases | 5-years NS | % of all cases | 5-years NS |
| Localized | 28 | 69.5 | 53.9 | 96.7 | 32.5 | 54.1 | 38.5 | 37 | 51 | 92.4 |
| Regional | 26 | 32 | 20.7 | 51.9 | 28.8 | 32.8 | 18.8 | 25.5 | 26 | 55.7 |
| Distant | 36 | 5.5 | 18.3 | 6.6 | 38.7 | 4.5 | 41.7 | 1.5 | 12 | 5.5 |
| Unknown | 10 | 23.4 | 7.2 | N/A | 11.9 | 37.8 | 1 | 10.5 | 11 | 49.2 |

Sources: [1]SEER 18 (2010-16); [2]personal comm. (2009-11); [3]NSW, ICBP SURVMARK-2 (2012-14); [4]cijfersoverkanker.nl (2010-14); [5]Korea National Cancer Incidence Database data 33; 5-yr NS: 5-year net survival; N/A: not available.

## CONCLUSION

In 2018, more than 1 million gastric cancer cases occurred globally of which 853,000 were at non-cardia sites. The main burden continues to fall in many countries globally, however gastric cancer remains a major challenge to public health on a global scale. This is mainly due to the absolute number of new cases which will stay stable or continue to grow in the foreseeable future, driven by population growth and aging as well as the increases seen in the incidence rates in younger generations in some countries. While these potential changes in the epidemiology of gastric cancer warrant continuing examinations and further research, urgent action in terms of cancer control is required from all countries given its substantial global burden, by, for example, including it in their national cancer control programmes with detailed assessments of human and economic impacts of prevention strategies.

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# Screening for gastric cancer in Europe: Is it feasible and useful?

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## BACKGROUND

Despite a uniform decrease in the incidence of gastric cancer (GC) in the last few decades, it remains one of the leading causes of cancer-related deaths worldwide [1]. In Europe, in 2012 alone, nearly 140,000 cases of GC were diagnosed, and approximately 107,000 people died of GC, according to the European Network of Cancer Registries (ENCR)[2]. GC diagnosis is related to poor survival (5-year survival <30% in most European countries) because at the time of presentation, most patients are diagnosed with advanced-stage disease. In contrast, early-stage GC has an excellent prognosis (5-year survival rates of >90%) and can often be treated with minimally-invasive, organ-sparing modalities, such as endoscopic resection [3].

Non-cardia GC (NCGC) subdivded into two histological subtypes - intestinal and diffuse according to Lauren's classification [4] - accounts for the vast majority of cancer cases within the stomach. *Helicobacter pylori* (*H. pylori*) infection is the most significant risk factor for GC, regardless of its histological class. Other conditions, such as older age, high salt intake, a diet low in fruits and vegetables, smoking, and family history, are additive risk factors if concomitant with *H. pylori* gastritis [5].

The development of intestinal-type NCGC is characterized by a stepwise progression described by the Correa cascade - an inflammatory-driven pathway typically initiated by the *H. pylori* infection. The inflamed gastric mucosa then undergoes several premalignant stages: from chronic atrophic gastritis to intestinal metaplasia,

dysplasia, and eventually, intramucosal cancer [6]. This multistage process provides a unique opportunity for screening and timely intervention when the disease is still at a benign stage.

On the contrary, the diffuse-type of NCGC does not offer a similar opportunity, as no such stepwise process in the oncogenic cascade has been documented. Despite a less well understood pathogenesis, the development of these tumors can also be attributed to *H. pylori* infection, which makes this organism a common ground in gastric carcinogenesis [7]. Overall, *H. pylori* is responsible for ~90% of the global burden of NCGC [8] and is increasingly recognized as the primary target of GC prevention strategies. However, in order to adopt and implement such strategies, a series of individual considerations need to be made.

## THE RATIONALE FOR GASTRIC CANCER SCREENING

A variety of factors must be considered when the implementation of a population-wide cancer screening program is posited, the most important of which are the country's demographic profile and the local burden of the disease of interest. In this context, the age-standardized incidence rate (ASR) is a commonly used parameter [9]. As any screening program must be tailored to disease burden, ASR characterizes the different risk levels in a given population. In terms of GC, three risk areas can be determined (*table 1*):

- High-risk areas: ASR ≥20 per 100,000 person-years (p-y); e.g., Japan, Korea, China;
- Intermediate risk areas: ASR ≥10 and <20 per 100,000 p-y; e.g., Portugal, Lithuania, Romania, Slovenia;
- Low-risk areas: ASR <10 per 100,000 p-y; e.g. USA, UK, Sweden, Germany.

At present, population-wide screening for GC is performed only in high-risk areas, such as Japan and South Korea. In Japan, with an estimated ASR for NCGC of 25.5 per 100,000 p-y [1], health authorities introduced the first national screening program in 1983. Initially, the program was based on barium gastrography; however, since 2017, it also includes annual endoscopy in individuals ≥50 years of age [10]. Similarly, in Korea, the National Cancer Screening Program recommends biennial upper gastrointestinal series or endoscopy for adults aged 40 years and older [11]. Although there is little evidence showing the influence of these programs on the outcome of GC, a recent meta-analysis indicated that endoscopic screening could lead to a 40% risk reduction in GC mortality (RR, 0.60; 95% CI, 0.49–0.73) in high-risk Asian countries [12].

On the contrary, in countries with a low GC incidence, there is no rationale for endoscopic screening, and it remains debatable in countries with intermediate risk. This raises the question: what should the appropriate GC screening strategy be, if any, in Europe?

TABLE 1. Summary table of established and postulated screening strategies for gastric cancer in different risk areas.

<table>
<tr><th>Low-risk areas<br>(ASR <10 per 100,000)</th><th>Intermediate risk areas<br>(ASR ≥10 and <20<br>per 100,000)</th><th>High-risk areas<br>(ASR ≥20 per 100,000)</th></tr>
<tr><td colspan="2">Targeted GC screening for at-risk individuals<br>(postulated and potentially cost-effective)</td><td>Primary GC screening<br>(established and cost-effective)</td></tr>
<tr><td colspan="2">H. pylori "Screen-and-treat" within at-risk individuals<br>(e.g., family history of GC, precancerous gastric lesions)</td><td>H. pylori "screen-and-treat"<br>within general population</td></tr>
<tr><td>Serological testing (serum pepsinogen) in high-risk individuals (e.g., smoking men over 50 years of age)</td><td>Upper GI endoscopy in FOBT-positive CRC screening individuals</td><td rowspan="3">Primary imaging screening (upper GI endoscopy / gastrography) in individuals ≥40(50) years old.</td></tr>
<tr><td colspan="2">Stool antigen H. pylori testing combined with a FOBT-based CRC screening program</td></tr>
<tr><td colspan="2">Serological testing (serum pepsinogen) coupled with CRC screening program</td></tr>
</table>

ASR: age-standardized ratio, CRC: colorectal cancer, GC: gastric cancer, FOBT: fecal occult blood test.

Applying a uniform screening strategy to Europe as a region presents challenges, as there is significant heterogeneity of the disease burden among individual country members, ranging from low to intermediate GC risk [13]. For instance, a recent systematic analysis showed that the ASR for GC varies from 10.5 cases per 100,000 (uncertainty intervals [UI]: 10.0-11.0) in Western Europe, to 17.7 cases per 100,000 (UI: 17.2–18.3) in the Eastern part of the continent [14]. On an individual country level, the incidence rate can vary from as high as 29.0 and 26.6 per 100,000 in Albania and Belarus to as low as 5.6 and 6.2 per 100,000 in Sweden and Switzerland, respectively [2].

There have been some initiatives in Europe to seek a feasible screening strategy in countries with an intermediate risk for GC. In particular, a recent cost-utility analysis has postulated that upper GI endoscopic screening can be cost-effective if combined with a screening colonoscopy in individuals between 50 to 75 years of age [13]. This is an interesting concept; however, most colorectal cancer (CRC) screening programs in Europe are based on fecal occult blood (FOBT) testing [15]. Therefore, this would be highly limiting, as the upper endoscopy screening would be available only to those who are offered a colonoscopy after a positive FOBT test. Moreover, as previously mentioned, it could only be cost-effective in countries where the incidence of GC is in the intermediate risk range. Only a few countries carry such a high burden of GC in Europe.



In practice, GC screening can be applied at different phases of disease evolution, from the earliest – *H. pylori* infection, through intermediate precancerous changes of the gastric mucosa – atrophic gastritis and intestinal metaplasia, to early-stage cancer itself. As with any population healthcare strategy, at-risk individuals should be identified with the least invasive, cheapest, and most patient-tolerable test possible. Currently, several screening strategies aiming to fulfill these criteria are being debated.

## *H. PYLORI* TESTING

*H. pylori* is categorized as a class I carcinogen according to the World Health Organization (WHO), and remains the primary risk factor for GC worldwide [16]. There are several non-invasive tests available in clinical routine for the detection of this pathogen, including *H. pylori* stool antigen test (HPSA), urea breath test (UBT), and serological tests (e.g., IgG to *H. pylori*). With these assays, a "screen-and-treat" approach is easily accessible, making this strategy a method of choice for primary GC prevention in high incidence areas [17]. Successful eradication therapy has been proven to decrease the degree of mucosal inflammation and prevent its progression to preneoplastic lesions [5]. In fact, the latest recommendations from the Kyoto consensus for high-risk regions support active and early screening for *H. pylori* infection before the consequences of chronic inflammation occur [18]. Overall, the recommendations generally propose that all individuals found to be infected should be offered eradication therapy unless there are competing considerations [18].

Furthermore, a very recent report from Taiwan has shown that HPSA testing could be successfully coupled with a CRC screening program [19]. In this nationwide study, eligible individuals were invited in a randomized fashion either to receive the standard fecal immunochemical test (FIT) or a FIT supplemented with an HPSA test. A positive HPSA result was followed by an eradication therapy, which was successful in 91.9% (95%CI 91.1 – 92.7%) patients (intention-to-treat [ITT] analysis). Interestingly, the addition of the HPSA test increased the screening program's participation rate by 13.9% (95%CI 13.4 – 14.4%), compared to FIT-only testing. It is also worth noting that *H. pylori* carriers had a higher rate of colorectal adenomas than non-carriers (adjusted RR: 1.15; 95%CI 1.03 – 1.28, P=0.01) [19]. Although the baseline results did not show any difference in the detection rates of early-stage GC between the groups, the long-term outcomes (e.g., the study's effect on GC mortality) are awaited. As most existing CRC screening programs in Europe are based on FOBT (particularly FIT) testing, this approach could be easily adaptable in a European setting.

## SEROLOGICAL BIOMARKERS



Both atrophic gastritis and intestinal metaplasia are associated with an increased risk of GC development. The prevalence and malignant potential of these conditions remain poorly characterized in Europe; however, a nationwide cohort study in the Netherlands has shown an annual progression rate of 0.1% and 0.25% for atrophic gastritis and intestinal metaplasia, respectively [20]. So far, endoscopy remains the mainstay for the diagnosis and surveillance of precancerous gastric conditions. In fact, European guidelines recommend endoscopic monitoring every three years for patients with the presence of extensive atrophy or intestinal metaplasia [21,22]. Emerging serological biomarkers, however, might provide a promising alternative for identifying precancerous gastric conditions.

Pepsinogen I (PGI) and pepsinogen II (PGII), both precursors of pepsin, are produced by the gastric mucosa and released into the gastric lumen and peripheral circulation [23]. PGI is secreted mostly by the chief and mucous neck cells in the fundic glands while PGII is also secreted in diverse types of glands all over the stomach". When atrophic changes develop in the gastric corpus, the level of PGI decreases while PGII levels remain relatively stable or may even increase. Hence, low serum pepsinogen PGI and/or PGI/PGII ratio is an accurate indicator of chronic atrophic gastritis and more advanced premalignant conditions, such as intestinal metaplasia, dysplasia, and even GC. Most studies on the utility of pepsinogen testing originate from high-risk areas for GC. Indeed, pepsinogen testing is already an established non-invasive GC screening method in Japan [24].

More recently, a few studies on the topic from low-risk areas have also been undertaken. A report from the USA showed that non-invasive screening with serum

pepsinogen could reduce gastric cancer mortality in high-risk individuals (actively smoking men aged > 50 years) and remain cost-effective [25].

In a German study, serum pepsinogen as a GC screening modality was assessed in patients undergoing colonoscopy (from various indications) [26]. A positive (i.e. abnormally low) serum pepsinogen result was significantly correlated with gastric atrophic changes, with a relative risk (RR) for this condition of 12.2 (95%CI: 6.3–23.5). Moreover, patients with a high-risk GC profile according to the Operative Link of Gastritis Assessment (OLGA; stages III and IV, respectively) [27] could be identified by serum pepsinogen assessment with a sensitivity of 75.0%, and a specificity of 82.2%, respectively [26]. The authors postulated that serological GC screening could be combined with a CRC screening program. Individuals with a positive pepsinogen test should be proposed an additional upper GI endoscopy in addition to screening colonoscopy [26].

Lastly, a multi-center study from the Netherlands and Norway showed that pepsinogen combined with a Gastrin-17 serological panel could be useful in stratifying patients with premalignant conditions of the stomach into those at either a higher risk or lower risk for malignant progression [28]. This study hints at the promising role of serological markers in tailoring endoscopic surveillance programs for high-risk individuals in low GC incidence areas.



Further studies on the topic have shown that serum levels of trefoil factor family proteins (TFF) may also be useful in serological GC screening. The best marker candidate from this group - TFF3 - showed a sensitivity of 80.9% and specificity of 81.0% for GC diagnosis and was superior to pepsinogen testing alone in the same cohort. Combining TFF3 with pepsinogen I/II testing may provide a more accurate non-invasive screening modality with increased accuracy for GC screening [29]. However, although promising, TFF testing as a screening method has not yet entered into clinical practice.

## CONCLUSION

As a region, Europe is rather heterogeneous in terms of GC burden with a gradually increasing incidence rate (general trend) in its Eastern parts, albeit with some exceptions (e.g., Portugal). Therefore, implementing a uniform GC screening program for the whole region could lead to an uneven allocation of resources. However, this should not discourage the active pursuit of prevention strategies since GC affects over 140,000 individuals in Europe every year and carries a dismal prognosis due to its advanced-stage presentation in most cases.

The "screen-and-treat" strategy for *H. pylori* infection has already been established in Europe and may have contributed to the continuing decrease of GC incidence in the region. So far, this strategy is mostly applied to patients with dyspeptic symptoms and has been proven to reduce the costs of dyspepsia work-up in general

healthcare 30. Considering this, more generalized testing (also including asymptomatic individuals) could remain cost-neutral for the healthcare segment. However, such a wide-ranged approach should be wisely balanced with potential pitfalls, such as increasing antibiotic resistance and possible adverse effects.

So far, the available evidence suggests that screening for GC in Europe could benefit specific populations and individuals. Those include patients with previous or active *H. pylori* infection, a positive family history for GC, or known gastric premalignant conditions 5. Emerging non-invasive serological markers and tests could help identify at-risk individuals and constitute a more patient-friendly alternative to replace endoscopy as a primary diagnostic modality.

Europe sorely lacks interventional healthcare studies on this topic. This critical medical and social demand could surely be the prelude to an exciting era of research, furthering the fight against a disease that remains a persistent threat to a large subset of the population throughout the continent.

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# Histology of gastric precancerous lesions

## What clinicians should know

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The vast majority of non-cardia gastric adenocarcinomas are related to *Helicobacter pylori* (*H. pylori*) infection. It is believed that most adenocarcinomas of the intestinal type [1] develop after a decades-long process of injury to the gastric mucosa through a sequence of phenotypic alterations known as the Correa cascade [2,3] (*figure 1*). It is also likely that a significant proportion of non-syndromic diffuse-type adenocarcinomas follow this pathway. Multifocal atrophic gastritis (non-metaplastic and metaplastic variants) and dysplasia are well-recognized precancerous lesions (*table 1*), with corresponding increasing risks of progression to cancer [4,5]. These lesions may be considered the 'field of cancerization' in which gastric cancer develops [6], and therefore, they should not be understood as mutually exclusive entities, but as morphological manifestations of the same precancerous condition. Although largely recognized as cancer precursors, their molecular alterations remain under intense investigation. The long-term nature of the gastric precancerous process offers an excellent period of opportunity for early detection of neoplastic lesions and ultimately for reduction of gastric cancer mortality. This chapter aims to summarize the most relevant concepts in histopathology of the precancerous process initiated by the two main etiologic factors of chronic atrophic gastritis: *H. pylori* infection and autoimmunity. This chapter excludes precursor lesions of cardia carcinomas, syndromic gastric carcinomas, and neuroendocrine neoplasms.

## THE CORREA PRECANCEROUS CASCADE

### Non-atrophic chronic gastritis

Upon colonization of the mucosa, *H. pylori* elicits an inflammatory reaction (gastritis) that may last decades unless successfully treated. The presence of polymorphonuclear neutrophils characterizes the acute inflammation episodes (acute gastritis or active gastritis) and is strongly associated with the presence of *H. pylori*. Lympho-

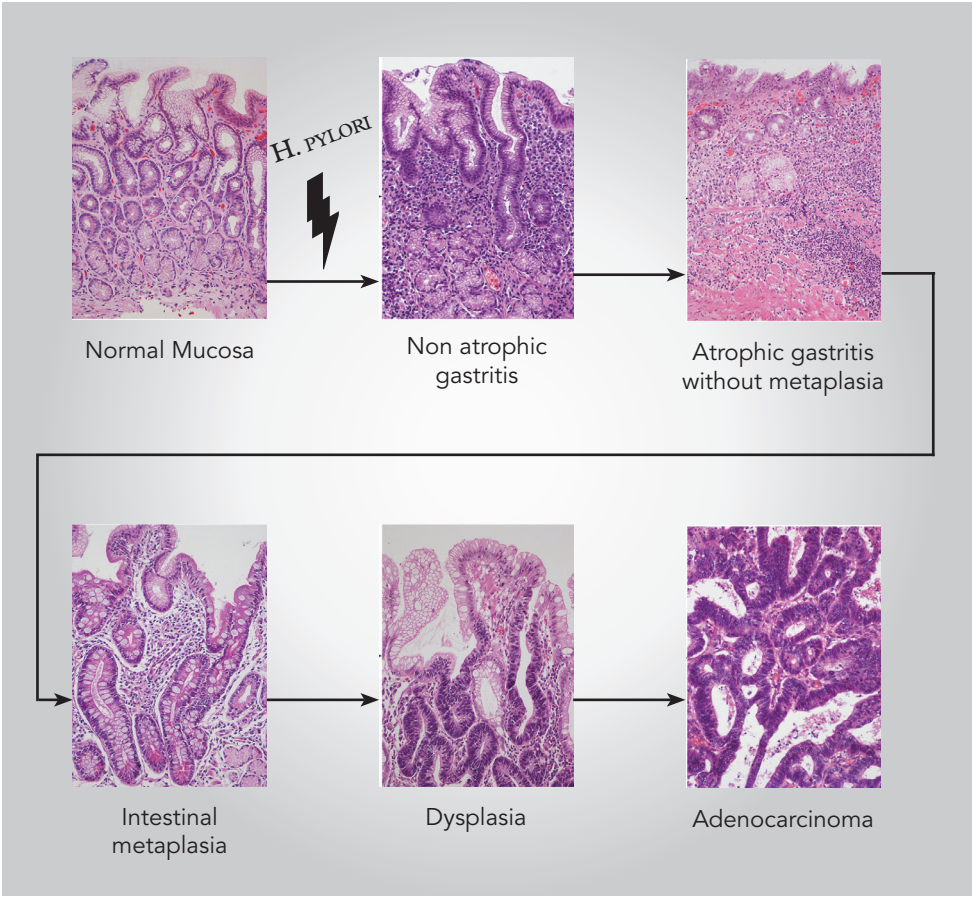


FIGURE 1. The Correa precancerous cascade.

cytes and plasma cells are the main components of the mononuclear leukocyte infiltrate in chronic gastritis, and lymphoid follicles are also frequently observed. *H. pylori* infection also stimulates epithelial proliferation, leading to elongation of glandular necks and foveolar hyperplasia. The infection occurs initially in the antropyloric region due to the less acidic environment being more favorable for the bacterium. Over time, or due to the effects of proton pump inhibitors in reducing gastric acidity, *H. pylori* may spread proximally colonizing the corpus mucosa. Despite inflammatory and epithelial proliferative alterations, the term non-atrophic gastritis reflects that the normal glandular epithelium is preserved, and this stage is not considered precancerous.

## Multifocal atrophic gastritis

Gastric atrophy is the loss of native glands and it represents a fundamental change reflecting chronic injury. When the inflammatory process persists over years or decades, individual glands or small groups of glands may become smaller in size or may completely disappear. They may be replaced by fibrotic tissue in the lamina propria (non-metaplastic atrophy) or by metaplastic epithelium (i.e. pseudopyloric metaplasia and/or intestinal metaplasia) (*table 1*). This entire process is called multifocal atrophic gastritis because occurs in a patchy fashion. It starts at the junction between the antrum and the corpus, mainly at the incisura angularis, as independent foci that coalesce and spread first along the lesser curvature and then to other parts of the stomach. Over time, larger areas of the antral and corporal mucosa may be affected [3]. Advanced stages of atrophic gastritis typically present a mixture of non-metaplastic and metaplastic areas in a patchy fashion.



TABLE 1. Gastric precancerous lesions.

| | |
|---|---|
| 1 | Multifocal atrophic gastritis |
| | a. Non-metaplastic: Shrunk/vanishing glands or loss of glands,<br>b. Pseudopyloric metaplasia (only in oxyntic mucosa),<br>c. Intestinal metaplasia:<br>i. Complete type (type I),<br>ii. Incomplete type (types II and III); |
| 2 | Dysplasia (non-invasive neoplasia, intraepithelial neoplasia) |
| | a. Indefinite for dysplasia,<br>b. Low-grade,<br>c. High-grade. |

### *Pseudopyloric metaplasia*

By definition, pseudopyloric metaplasia (also called antralization), only occurs in the oxyntic mucosa. It is characterized by loss of parietal and chief cells, which are replaced by epithelium with mucous phenotype, resembling the antropyloric glands (*figure 2*). In advanced stages of oxyntic atrophy, the specialized (parietal and chief) cells may be completely lost. Although pseudopyloric metaplasia may be easily identified in routine hematoxylin and eosin (H&E)-stained sections, in absence of a proper documentation of the anatomic location of a corpus biopsy specimen, this type of metaplasia may be overlooked. In such instances, a gastrin immunohistochemical stain may be useful in differentiating oxyntic from antral mucosa by demonstrating an absence of G cells in metaplastic oxyntic mucosa. A lesion resembling pseudopyloric metaplasia has been described in rodent models of human gastric disease and named spasmolytic polypeptide-expressing metaplasia. Spasmolytic polypeptide is the trefoil factor 2 (TFF2), which is normally expressed in the human mucosecreting glands in the antropyloric mucosa, in the Brunner glands, and in the mucous neck cells in the oxyntic mucosa. Pseudopyloric metaplasia consistently expresses TFF2 [7].



### *Intestinal metaplasia*

Intestinal metaplasia, on the other hand, is a lesion much easier to recognize in routine histological sections and can be observed in any area of the gastric mucosa. It is defined as the replacement of native gastric epithelium by epithelium resembling intestinal morphology. It has long been recognized that intestinal metaplasia is a very heterogeneous lesion, and multiple classifications have been proposed [8-11]. One of the most frequently used classifications recognizes two types: complete (or small intestinal) and incomplete (or colonic). Although initially based on the complete or incomplete presence of small intestinal digestive enzymes [10,11], discrimination between these two types has been widely adopted by pathologists on the basis of morphology on H&E-stained sections [12] (*figure 3*). The complete type is characterized by well-developed goblet cells alternating with eosinophilic enterocytes with well-defined brush border (representing absorptive microvilli), and Paneth cells are observed at the base of the crypts. Incomplete metaplasia shows goblet cells of varying size alternating with columnar cells containing intracytoplasmic mucin droplets, and absence of a brush border. In addition, the incomplete type tends to show a more irregular architecture.

Another classification, developed by Jass and Filipe [8,9], recognizes three types of intestinal metaplasia based on the mucins expressed: type I corresponds to the complete type, and types II and III are subclassifications of the incomplete type (*figure 4*). Special histochemical stains are required: the Alcian blue pH 2.5/periodic acid–Schiff (AB/PAS) technique discriminates between gastric and intestinal mucins. In turn, intestinal mucins can be sialic or sulfated, and are dif-

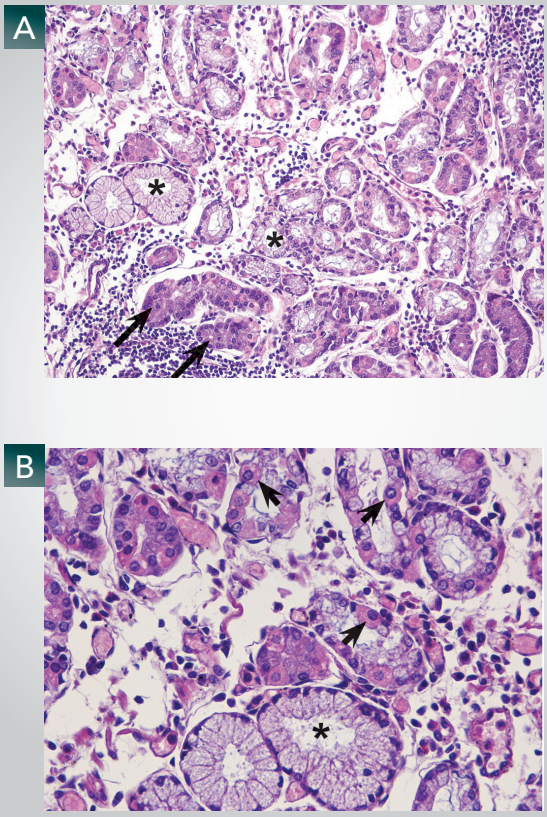


FIGURE 2. Chronic atrophic gastritis with pseudopyloric metaplasia. A) Corpus mucosa showing disorganized architecture and glandular structures with antral phenotype (pseudopyloric metaplasia; asterisks). There is severe loss of parietal and chief cells. Arrows show remaining chief cells at the base of the glands; B) at higher magnification, pseudopyloric metaplasia (asterisk) and scarce parietal cells (arrowheads) are observed. Hematoxylin and eosin; original magnifications, ×200 (a) and ×400 (b).

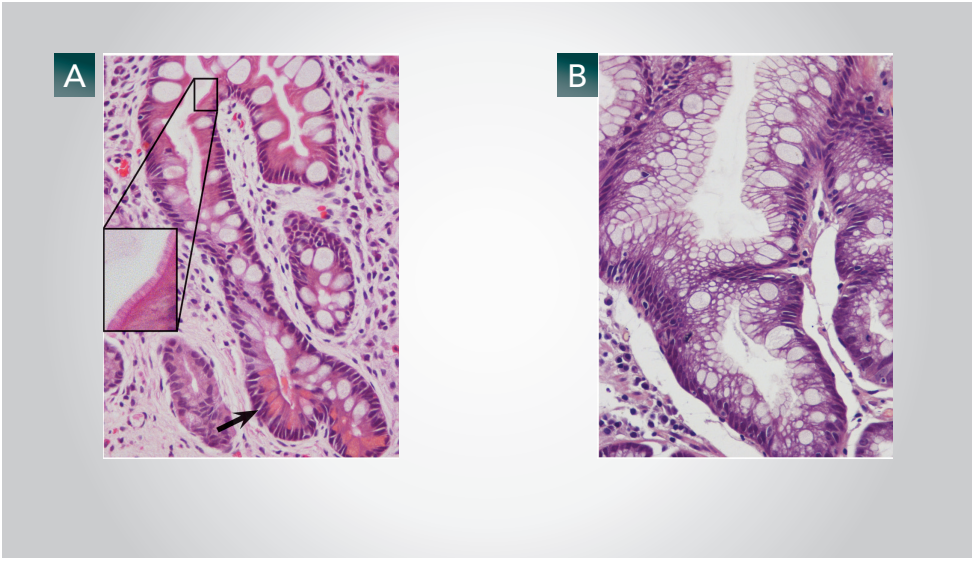




FIGURE 3. Intestinal metaplasia. A) Complete type, with well-defined goblet cells alternating with eosinophilic enterocytes displaying a brush border (inset) and Paneth cells at the bottom of the crypts (arrow); B) incomplete type, showing goblet cells and intracytoplasmic mucin droplets of varying sizes and shapes, and absence of a brush border. Hematoxylin and eosin; original magnification, ×400; inset, ×1,000. Reproduced from original publication 12, with permission.

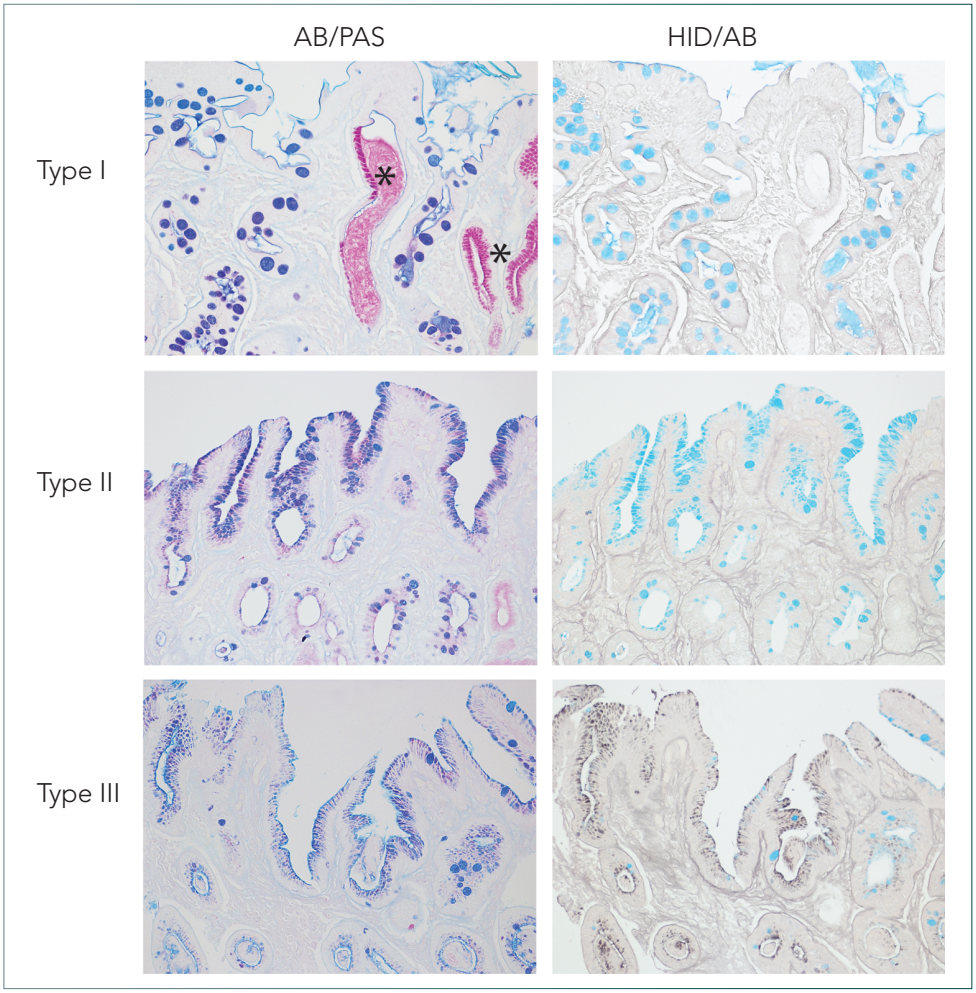


FIGURE 4. Intestinal metaplasia classification by Jass and Filipe [8]. Type I: with AB/PAS, goblet cells show a mixture of neutral (magenta) and acid (blue) mucins in goblet cells (yielding a purple color); in this image (left upper corner) a few normal gastric glands are stained magenta (asterisks). With HID/AB, the type I shows only sialomucins (blue) in goblet cells. Incomplete types II and III with AB/PAS show a mixture of gastric (magenta) and intestinal (blue) mucins in goblet and columnar cells. With HID/AB, the type II shows only sialomucins (blue) in goblet and columnar cells, and the type III displays predominantly sulfomucins (brown mucin droplets) in columnar cells. AB/PAS, Alcian blue (pH 2.5)/periodic acid-Schiff; HID/AB, high-iron diamine/Alcian blue; original magnification, ×200. Reproduced from original publication [33] with permission.

ferentiated with the high-iron diamine (HID)/AB technique. The type I displays mucins only in goblet cells; the type II may display sialomucins or a mixture of gastric and sialomucins in goblet cells and intermediate columnar cells; and the type III is characterized by the predominant presence of sulfomucins in the columnar intermediate cells. Any combination of the three types may be observed in a single biopsy.

The significance of these classifications is based on their utility to predict the risk of gastric cancer. A large body of evidence supports that the incomplete type is associated with higher synchronous or prospective gastric cancer risk than the complete type [8,13-17]. Therefore, the presence of incomplete type was proposed as a more advanced step in the precancerous cascade [2]. Using Jass and Filipe classification, the type III has shown the highest association with gastric cancer [8,13]. However, the HID/AB technique involves potentially toxic diamine reagents and has been discontinued in many laboratories worldwide, being reserved exclusively for research purposes.

For practical purposes, the differentiation between complete and incomplete may be useful, and in most cases can be made using routine H&E-stained sections. It should be clarified, though, that the images in *figure 3* are very well-defined examples, but as mentioned, intestinal metaplasia is a very heterogeneous lesion and sometimes subtyping based on routine staining is not possible due to ambiguous/unclear features. In such instances, the AB/PAS technique (which is performed with relative regularity in histopathology laboratories) may be useful for differentiating complete versus incomplete types. Extensive intestinal metaplasia usually presents a combination of complete and incomplete subtypes. Despite the evidence, the utility of intestinal metaplasia subtyping as a marker of gastric cancer risk has not been widely adopted in clinical practice. It has been observed that the extent of atrophic changes is directly related with the presence of the incomplete type [13,17,18]. Therefore, when the extent of atrophy can be assessed applying staging systems for risk assessment (see below), subtyping of intestinal metaplasia may not provide additional useful information.



## ASSESSMENT OF GASTRIC CANCER RISK BASED ON THE EXTENT OF ATROPHIC CHANGES

The updated Sydney system for the classification of gastritis [19] was widely accepted in clinical practice and has provided guidance for grading of histopathological variables and information regarding the etiology of gastritis according to the topography. It also proposed a 5-biopsy protocol (2 antrum and 2 corpus, from lesser and greater curvature each, and one from the incisura angularis) for an adequate representation of the gastric mucosa [19]. Biopsy samples should be submitted in at least 2 separate containers: antrum (including incisura biopsy) and corpus. Subsequently, based on the consensus that the extent of atrophic

changes is related with the gastric cancer risk, a group of pathologists and gastroenterologists created the Operative Link on Gastritis Assessment (OLGA) staging system. The risk of developing neoplasia is categorized in stages: 0-II are low-risk, and III-IV are high-risk. Stages are assigned by combining the extent of antrum and corpus atrophic changes (including all variants of atrophy: non-metaplastic, pseudopyloric and intestinal metaplasia) (*figure 5*) [20,21]. A second system, the Operative Link on Gastritis Assessment based on Intestinal Metaplasia (OLGIM), was then proposed based on the high interobserver agreement for the diagnosis of intestinal metaplasia [22]. The OLGIM system uses the same stages, but with intestinal metaplasia as the only histopathology parameter. Although both systems have been validated [17,23,24], it has been observed that by focusing on intestinal metaplasia alone, the OLGIM system is less sensitive in identifying individuals at high risk, by down-staging some patients who should be offered follow-up [25].

| Atrophy score | | Corpus | | | |
|---|---|---|---|---|---|
| | | Score 1 | Score 2 | Score 3 | Score 4 |
| Antrum | No atrophy (score O) * | Stage 0 | Stage I | Stage II | Stage II |
| | Mild atrophy (score 1) * | Stage I | Stage I | Stage II | Stage III |
| | Moderate atrophy (score 2) * | Stage II | Stage II | Stage III | Stage IV |
| | Severe atrophy (score 3) * | Stage III | Stage III | Stage IV | Stage IV |

FIGURE 5. The OLGA staging system. Reproduced from original publication [20] with permission. * including incisura angularis.

Some caveats in the application of these systems are:

1. In the OLGA system, the perpendicular orientation and full thickness of the mucosa is required, specifically for the scoring of atrophy without metaplasia, although not so critical for scoring the metaplastic variants. In the OLGIM system, the orientation or full thickness of the biopsy is less critical.
2. The OLGA stage of an individual cannot be lower than the OLGIM stage since intestinal metaplasia is also included in the OLGA system [26]. The misinterpretation of OLGA as only assessing atrophy without metaplasia has caused considerable confusion in the literature.
3. Both systems use an average (although antrum and corpus separately) of the extent of the atrophic lesions, so the OLGA or OLGIM stage of an individual should not be used as the only parameter for endoscopic surveillance decision. As an example, an individual with intestinal metaplasia in each of the five biopsy samples still could be classified in a low-risk OLGIM stage.

## DYSPLASIA

Gastric dysplasia (synonyms: intraepithelial neoplasia, non-invasive neoplasia, adenoma) is a neoplastic process limited to the epithelial layer and is associated with a higher risk of synchronous or metachronous gastric cancer than the previously discussed lesions [4,5]. Dysplasia arises most frequently in the antral compartment, but in the presence of extensive atrophic changes, dysplastic lesions may occur in any gastric location [27]. Morphological features include both cytological and architectural abnormalities without disruption of the epithelial basement membrane and without invasion to the lamina propria. Multiple classification systems exist, but as a consensus, dysplasia is mainly graded as: indefinite for dysplasia, low-grade, or high-grade [27-30].

### Indefinite for dysplasia

One of the major challenges in the diagnosis of dysplasia is the differentiation from reactive or regenerative epithelial changes. The term indefinite for dysplasia is used when atypical epithelial changes cannot be definitively categorized as dysplastic. Cytological atypia (without or with architectural alterations) may be observed in the presence of erosions, ulcerations, or marked inflammation. In addition, the Padova classification [29] describes two specific lesions in this category: hyperproliferative intestinal metaplasia and foveolar hyperproliferation. Although both lesions may be observed in the setting of *H. pylori*-induced gastritis, the latter may also arise as a reactive change to a variety of chemical agents, such as bile acid or nonsteroidal anti-inflammatory drugs. Furthermore, certain technical issues, such as cautery artefact or poor tissue fixation can make interpretation difficult. In all these situations, indefinite for dysplasia is an appropriate temporary diagnosis, and a repeat biopsy (after medical therapy, if necessary) is indicated[29].

### Low-and high-grade dysplasias

In low-grade dysplasia, the nuclei are enlarged and hyperchromatic, frequently with 'cigar-like' appearance and pseudostratification. There is mucin depletion, increased nuclear/cytoplasmic ratio, and occasional mitosis. The nuclei are basally located and maintain the polarity with respect to the basement membrane, and there are minimal architectural changes (*figure 6A and B)*. High-grade dysplasia shows a more disorganized epithelium, with larger, plump, and more irregular nuclei of variable size, some of them occupying the upper halves of the cells. (*figure 6C and D*) Other characteristics are prominent amphophilic nucleoli, loss of cell polarity and increased mitotic activity. Architectural changes may consist of irregular or branched tubular structures, or a cribriform pattern. No stromal invasion is allowed in the diagnosis of dysplasia. It has been long recognized that discrepancies exist in nomenclature of neoplastic lesions

between western and Japanese pathologists. For western pathologists, invasion is the hallmark of carcinoma. In Japan, carcinoma is diagnosed based on definitive neoplastic epithelium, even without invasion [30]. The diagnosis and grading of dysplasia is subject to significant interobserver variation; therefore, a second opinion is strongly advisable.

According to the recent WHO classification of tumors of the digestive system,[27] although the terms 'dysplasia' and 'intraepithelial neoplasia' are still considered acceptable for lesions in certain anatomical locations, the term dysplasia is preferred for lesions in the tubal gut, whereas intraepithelial neoplasia is preferred for those in the pancreas, gallbladder and biliary tree. The term 'carcinoma *in situ*' is not recommended, instead this term is included in the category of high-grade dysplasia [27].

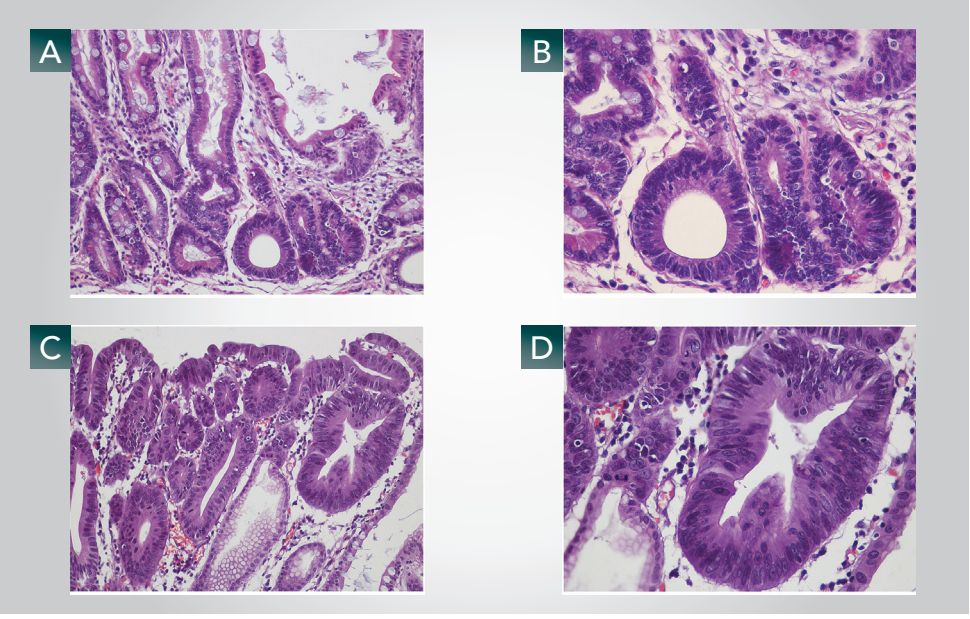


FIGURE 6. A-B) Low-grade dysplasia. At lower magnification (A), a small focus of low-grade dysplasia is observed in a background of intestinal metaplasia. B) Higher magnification of the dysplastic glands, with hyperchromatic, basally located nuclei, with 'cigar-like' appearance and pseudostratification. C-D) High-grade dysplasia replacing most of the epithelium observed (C) with the exception a few metaplastic glands in the lower right area. At higher magnification (D), larger and plump nuclei of variable size are observed, some of them occupying the upper halves of the cells and displaying prominent nucleoli. Hematoxylin and eosin; original magnification, ×200 (A, C); ×400 (B, D).

## AUTOIMMUNE GASTRITIS

Autoimmune gastritis is a type of immune-mediated chronic atrophic gastritis of the oxyntic mucosa where the parietal cells are the primary target. It is characterized by the presence of antibodies against parietal cells and/or intrinsic factor [31].The pathogenesis of this condition is not completely understood, but there is evidence that *H. pylori* infection may represent a trigger of autoimmunity in some cases. Autoimmune gastritis represents a preneoplastic condition, as patients with pernicious anemia (its most recognized late-stage clinical manifestation) have a high risk of developing either type 1 gastric neuroendocrine tumors [27] or gastric adenocarcinomas [32]. The typical histological manifestation of autoimmune gastritis is a corpus-predominant atrophic gastritis, a pattern different from the most common antral involvement in *H. pylori*-associated gastritis. Histopathological features vary according to the stage of the disease and include a predominantly lymphoplasmacytic infiltrate in the lamina propria and presence of foci of lymphocytes infiltrating glands. Atrophic changes include a variable degree of loss of parietal and chief cells, and epithelial metaplastic transformation (pseudopyloric, intestinal, and pancreatic acinar). In advanced stages, there may be enterochromaffin-cell-like hyperplasia and type 1 neuroendocrine tumors, indicating a state of hypergastrinemia. In the corresponding antral mucosa, hyperplasia of gastrin-producing (G) cells is usually observed [27].



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# *Helicobacter pylori* infection and gastric precancerous lesions

## Don't be too late to eradicate!

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In the past, it was thought that in contrast to other organs, the stomach was evolving histologically and physiologically over the years , leading to the opinion that it was a normal evolution. The different steps were well described by Correa 1 and later the essential cause of this evolution was discovered: the bacterial infection by *Helicobacter pylori*.

However, this cascade of events does not apply to the evolution of cardia gastric cancer (GC) or the diffuse type non-cardia GC according to the Laurén histological classification.

In this chapter, we will review the role of *H. pylori* in the different steps that lead to gastric precancerous lesions, the other factors that contribute to this evolution, and the impact of *H. pylori* eradication, including the treatment used and the cost-effectiveness of this approach.

## EVOLUTION OF *HELICOBACTER PYLORI* INFECTION

### From epidemiology to etiologic discovery

As early as 1975, i.e. before the discovery of *H. pylori*, Correa *et al.* proposed a model for GC pathogenesis, which could apply to most GC, those of the intestinal type.

The different steps were chronic gastritis, gastric atrophy, intestinal metaplasia (IM) followed by dysplasia and early GC. They anticipated that the first step already began in the first decade of life and that the mutagen involved could be a nitroso compound. This sequence of histological events was named the Correa cascade 1.

Later *H. pylori* was discovered and shown to be the essential cause of this cascade of events 2.

## The role of *Helicobacter pylori*

*H. pylori* is indeed acquired early in life, essentially but not exclusively in the family, mainly by oral-oral contamination or vomit, and provokes an acute gastritis which evolves to chronic gastritis [3].

Most individuals are not able to get rid of the bacteria spontaneously as these bacteria are located "outside" of the body, in the mucus layer lining the gastric epithelium.

This infection induces limited or no symptoms and, given its occurrence at a young age, most people consider the few symptoms that they may have as normal. Indeed, *H. pylori* is even considered to be beneficial in childhood because it contributes to the maturation of the immune system [4]. Only a few children develop ulcers, necessitating a treatment [5].

After several years and sometimes decades, the gastric mucosa tends to become atrophic, altering the physiology of the stomach, and intestinal cells may appear focally.

*H. pylori,* and especially its oncoprotein CagA, are able to reprogram epithelial cells and activate properties of stemness of progenitor and stem cells [6]. Accumulation of DNA damage can happen during the close contact between *H. pylori* and host cells [7]. When IM occurs, the role of *H. pylori* which cannot colonize these cells becomes of secondary importance compared to other additional factors which will lead to dysplasia and GC.



## Other factors

While the role of *H. pylori* is essential, and at the origin of around 90% of GC [8], the remaining 10% are caused by the Epstein Barr virus [9], and other factors, both genetic and environmental, are important contributors.

First, it must be underlined that even if all *H. pylori* strains are able to induce chronic gastritis, they are not equal with regard to their pathogenicity factors. Among these factors, there are variations in the attachment factors, the amount of cytotoxin production ranging from none to a lot according to the genotype [10], and even more importantly a pathogenicity island, namely *cag*, which has important proinflammatory properties and is not present in all strains, or is partly deleted [11]. Moreover, in the last steps of the carcinogenic process, the importance of gastric microbiota is crucial. Different bacteria can colonize the stomach which is now less acidic, including bacteria that produce N-nitroso compounds [12] and acetaldehyde [13], which are well known carcinogens.

It has also been shown that the host genotype, especially with regard to IL-1β and other cytokines [14], may influence the degree of inflammation and gastric acid inhibition.

Finally, dietary factors and drugs have an important impact. A salty diet may itself induce gastric atrophy, consequently acting as a synergistic factor with *H.*

*pylori* infection [15]. Iron deficiency and a lack of vitamins and anti-oxidants have also been implicated [16]. In contrast, a diet rich in vitamins is considered to be protective. Regarding drugs, long term use of proton pump inhibitors (PPI), which permanently decrease the acidity, are also possible risk factors.

The first progress in terms of histological evaluation of gastric lesions was the publication of the Sydney system, which grades the activity, inflammation, atrophy, IM and the presence of *H. pylori*, separately. [17]. Another crucial step was the development of the OLGA [18] and OLGIM [19] staging systems, which have an important clinical value because they provide information on the risk of evolution of premalignant lesions to GC.

Another point is the risk related to the so-called incomplete IM (Type III). This typing, based on the mucin profile [20], is not used systematically but may be an important factor as observed in some studies [21].

## *HELICOBACTER PYLORI* ERADICATION AND ITS IMPACT

### *Helicobacter pylori* eradication



Since *H. pylori* is a bacterium, it is possible to eradicate it with antibiotics, but it is not easy. It is necessary to add antisecretory drugs, namely PPI, to increase the gastric pH to allow the activity of most antibiotics or, even better when available, potassium-competitive acid blockers (P-CAB), such as vonoprazan [22].

Clinical trials performed in the 1990s showed that a combination of two antibiotics was necessary, i.e. clarithromycin and amoxicillin or clarithromycin and metronidazole [23]. This triple therapy (with a PPI) has been used worldwide but its success decreased progressively at the beginning of the century, due to an increase in clarithromycin resistance [24]. To continue giving empiric treatment, quadruple therapies using either clarithromycin-amoxicillin-metronidazole + PPI [25] or tetracycline-metronidazole-bismuth salts + PPI [26] have therefore been recommended. However, they are not in line with the WHO recommendations for prudent use of antibiotics [27] and the treatment generates more immediate adverse events than triple therapies. In addition, mid- and long-term effects like selection of antibiotic resistance in other bacteria and changes in the gut microbiota are greater than with triple therapies. Therefore, the current policy, when possible, is to use the triple therapy, guided by antimicrobial susceptibility testing (AST) [28].

Commercially available kits exist today, allowing for the detection of *H. pylori* and its eventual resistance to clarithromycin, the most crucial antibiotic in this respect. These kits are based on real-time PCR, which is convenient to use and gives quick and precise results [29]. Based on the AST result, clarithromycin can still be administered in 70-80% of the cases according to the region in Europe [24]. However, this

guided triple therapy has to be optimized, i.e. it must include: 1) the most effective PPI: esomeprazole or rabeprazole, which are not modified by the hepatic enzyme: CYP2C19, and prescribed at a higher dose than before, 2) the prescription of 1g amoxicillin three times a day instead of two to avoid a time lapse without amoxicillin in the gastric mucus, given the pharmacokinetics of the antibiotic [30], and 3) the treatment must be prolonged to two weeks (*table 1*).

In case of failure which should not exceed 10% of the cases, there is still the possibility to use a quadruple therapy, preferably one using bismuth. For those allergic to penicillin, amoxicillin must be replaced by metronidazole in the triple therapy.

TABLE 1. Proposition of eradication treatment for *Helicobacter pylori*.

| | First line treatment |
|---|---|
| | guided by AST for clarithromycin |
| A | *if clarithromycin susceptible (or absence of 23S rDNA mutation detected by RT-PCR)*<br>esomeprazole or rabeprazole (double dose) - clarithromycin (500 g x 2) - amoxicillin (1 g x 3) for 14 days |
| B | if clarithromycin resistant<br>Pylera® - omeprazole for 10 days |
| | **Second line treatment** |
| | after guided treatment A: Pylera®* - omeprazole for 10 days<br>after treatment B - test for levofloxacin |
| C | *if levofloxacin susceptible*<br>esomeprazole or rabeprazole (double dose) - amoxicillin (1 g x 3) - levofloxacin (500 mg x 2) for 14 days |
| D | *if levofloxacin resistant*<br>esomeprazole or rabeprazole (double dose) - amoxicillin (1 g x 3) - metronidazole (500 mg x 2) for 14 days |
| | **Third line treatment** |
| | consider Talicia® |

AST: antimicrobial susceptibility testing.

* Pylera® contains per capsule: tetracycline 125mg-metronidazole 125mg-bismuth sub citrate 140mg. Recommended 3 capsules 4 times per day.

**Talicia contains per capsule omeprazole 10mg - amoxicillin 250mg - rifabutin 12.5mg

## Impact of *H. pylori* eradication according to the mucosal status

When the eradication treatment is given at the chronic gastritis stage, a quick improvement in histology occurs. The bacteria and the inflammatory activity disappear, but it may take months to observe the disappearance of the inflammatory components and the re-establishment of a normal mucosa. In a mouse experiment, we observed that resveratrol, with its anti-inflammatory properties, speeds up the process 31.

When the treatment is given at the gastric atrophy stage, the process is much slower and may take years. Rokkas *et al.* carried out the first systematic review and meta-analysis on the reversibility of gastric atrophy after *H. pylori* eradication. They found 8 studies with an at least one-year follow-up, with the majority being less than ten years. There was a beneficial effect both on the antrum and the corpus, the pooled OR with a 95% confidence interval (CI) being 0.554 [0.372-0.825), p=0.004 for antrum atrophy and 0.209 [0.081-0.538], p <0.001 for corpus atrophy 32.

In a second meta-analysis that included 26 studies 33, they found the same results on GC prevention , without significant heterogeneity. One limitation of this study was that 24 of the studies were performed in East Asian countries. However, *H. pylori* eradication did not have an effect on the evolution towards GC in either publication, when the histological examination at baseline showed either IM or dysplasia.

More recently, very long term follow-ups studies are appearing in the literature and show that even under such circumstances it is possible to see a regression of the GC risk, and so a controversy was born. If we take the analogy of smoking as a risk factor for lung cancer, it is possible to see a decrease in the risk of lung cancer to the baseline level only after more than 20 years of not smoking 34. It is therefore conceivable that such a long delay without *H. pylori* infection may also be necessary to decrease the risk of GC to the baseline level, and more long term follow-ups studies are needed to provide a definitive answer to the question.

## How to manage *H. pylori* eradication at the population level?

A remaining question is whether an organized screening for *H. pylori* infection and its associated lesions in the general population would be beneficial. The current status is that it can be cost effective only in countries with a high prevalence of infection and a high incidence of GC, essentially in East Asia. Furthermore, the benefit of an immediate expense will only be seen a long time afterward 35. The pragmatic approach in most European countries is to test for *H. pylori* in all patients undergoing upper digestive endoscopy that are older than 50, and to treat them if positive. In some countries a test and treat approach using non-inva-

sive tests is proposed for younger patients. The limitation is that GC can develop with minimal symptoms and therefore *H. pylori* eradication may occur too late. In this situation, there are recommendations to perform an endoscopy follow up at regular intervals.

In other situations the proposal was to combine the colorectal cancer detection program with screening for *H. pylori* and premalignant lesions. A non-invasive test using *H. pylori* serology and evaluation of the Pepsinogen I/II ratio is used to select those for whom an upper digestive endoscopy will be performed.

## CONCLUSION

We can conclude that *H. pylori* eradication is always beneficial but to bring the most benefit, it must not be carried out too late in life. However, the current recommendation is not to eradicate during childhood, but ideally in young adults, before they have children. This, in turn, would limit the transmission to the younger generations. It can obviously be performed later but the risk is that it takes decades for the mucosa to get back to normal, especially when it attains the grade of IM, so the sooner the better!



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# Non-invasive tests for the detection of gastric atrophy: What is really useful?

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## THE APPLICATION OF NON-INVASIVE TESTS FOR GASTRIC ATROPHY

The 'gold standard' for the detection of gastric mucosal atrophy is endoscopy – either with detailed biopsy assessment (the Western approach) or by thorough visual inspection (the typical approach in the East). The clinical application of non-invasive testing for the detection of gastric atrophy generally includes one of the following: 1) for selecting symptomatic patients for endoscopy, and therefore avoiding unnecessary procedures, or 2) as a general population-based screening of asymptomatic individuals to identify those at an increased risk. Although non-invasive testing for atrophy has been available for decades, numerous guidelines and recommendations have indicated the rationale for the use of such tests (mainly pepsinogen testing). At this stage, no country has yet introduced population-based testing. The available evidence and guideline recommendations will be reviewed in this chapter; in addition, a brief discussion of emerging testing modalities will be provided.

## THE RELEVANCE AND APPROACHES FOR PEPSINOGEN DETECTION

Pepsinogens are the most studied indirect markers for gastric mucosal atrophy.

In 1982, Michael Samloff was the first to propose the clinical use of serum pepsinogen I as "a serological biopsy for gastric mucosa" [1]. Pepsinogens are pepsin pro-enzymes that can be measured in blood as indirect markers of gastric mucosal changes [2]. Two isozymogens, pepsinogen I (PgI) and pepsinogen

II (PgII), are produced in different parts of the stomach [3]. PgI production is exclusively limited to acid-secreting glands of the gastric corpus (proximal stomach), whereas PgII production is widespread in diverse types of glands throughout the stomach, as well as Brunner glands of the duodenum [4]. *Figure 1* summarizes the physiology and anatomical site of production of pepsinogen I, pepsinogen II and gastrin 17. Thus, mucosal atrophy affecting the gastric corpus leads to decreased levels of PgI, while PgII levels tend to be relatively stable. In particular, the presence of mucosal inflammation, also related to *H. pylori* infection, may increase the levels of both PgI and PgII [5, 6] and thus in some cases result in normal PgI values when both atrophy and inflammation are present [7]. To account for this draw-back, a decreased ratio of PgI to PgII (PgI/PgII) is considered to be the best serologic marker of gastric atrophy [8].



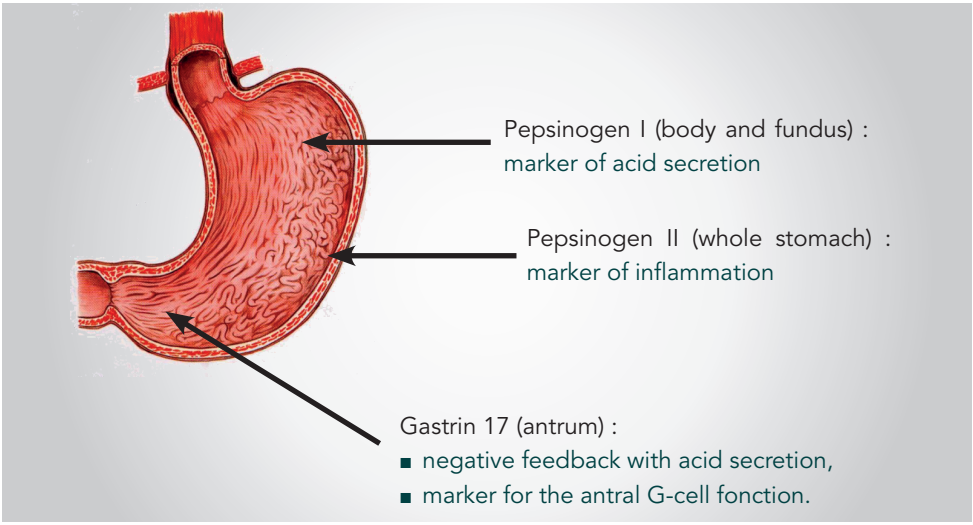



FIGURE 1. Functional anatomy of serological markers of gastric mucosa.

It should be noted, that different methods can be used for pepsinogen detection (latex-agglutination, ELISA, chemiluminescent enzyme immune assay). While there is a good correlation between results obtained with different methods [9], the results may appear different when absolute values are considered. Therefore, the cut-off values have to be decided specifically for the method used, and potentially, also adjusted in different populations.

Several meta-analyses have addressed the issue of the accuracy of pepsinogen testing for the detection of precancerous gastric lesion.

The initial meta-analysis by Dinis-Ribeiro *et al.* [2] included 42 data sets, including population-based screening studies accounting for 296,553 individuals.

Multiple studies from Asia (predominantly Japan) were included. Eight studies were considered in the evaluation of the performance of pepsinogens for corpus atrophic gastritis detection. However, because of heterogeneity, in particular, the use of different cut-offs, pooled analysis was not possible.

The meta-analysis by Huang *et al.* [10] in 2015 demonstrated good correlation between decreased pepsinogen levels and atrophic gastritis, and the authors succeeded in calculating a pooled sensitivity of 69% (95% CI 55 – 80) and specificity of 88% (95% CI 77 – 94), and ROC AUC of 0.83 (95% CI: 0.80-0.86) for PgI/PgII to detect atrophy. The authors concluded that serum pepsinogen levels have a potentially significant role in the identification of populations at high risk of gastric cancer and could be used for mass screening. It was also noted that there was great heterogeneity between studies, in particular using different methods for the quantification of pepsinogen levels.

The third metanalysis was published by Zagari *et al.* [2] in 2017, and in addition to pepsinogens it has addressed the role of the pepsinogen, gastrin-17 and *H.pylori* antibody combination for the detection of atrophic gastritis. Twenty studies that have used this detection panel (GastroPanel ®) with a total of 4241 subjects assessed the performance of the serological marker test for the diagnosis of atrophic gastritis regardless of the site in the stomach. The sensitivity was at 74.7% (95% CI: 62.0-84.3) and specificity at 95.6% (95%, CI: 92.6-97.4). With a prevalence of atrophic gastritis of 27% (median prevalence across the studies), the negative predictive value was at 91%. The authors have suggested that the sensitivity and specificity of the panel is higher than for pepsinogen and gastrin-17 serum assays separately.

The most recent meta-analysis has been published by Bang *et al.* [11] showing a sensitivity of 59%, specificity of 89%, odds ratio of 12, and 0. area under the curve at 0.81 for the cut-off values of PG I ≤70 ng/mL and PG I/PG II ratio ≤3 for the detection of corpus atrophic gastritis.

Thus, the accumulated evidence suggests moderate sensitivity, but relatively high specificity for pepsinogen tests to detect atrophic gastritis.

**Box. Practical hints**

- The PgI/PgII ratio should be used for diagnostic purposes instead of PgI alone because the use of a ratio compensates for the increase in pepsinogen levels caused by mucosal infection, in particular by *H. pylori.*
- Different methods are currently used for pepsinogen detection in clinical practice, including latex-agglutination, ELISA, CLEIA (chemiluminescent enzyme immune assay).
- Cut-off levels for either PgI of Pg I/II depend on the test-system (method) used, and should not be transposed between different methods (a common mistake), and may be adapted to the studied population.

## ABC (D) METHOD

Combined evaluation of pepsinogen levels and detection of the presence of *H. pylori* has been suggested by Miki and colleagues in Japan for population-based testing. Typically, serological detection of antibodies against *H. pylori* has been suggested for this purpose. Accordingly, patients are divided into the following groups (ABCD) (*table 1*).

TABLE 1. ABC(D) group definitions.

| | A | B | C | D |
|---|---|---|---|---|
| Pepsinogens | Normal | Normal | Decreased | Decreased |
| *H. pylori* | Absent | Present | Present | Absent |

As demonstrated by Watabe *et al.* [12] in a 4.5 year follow-up of 7,000 patients, the highest risk score was in the "D" group, which could be explained by the fact that in the natural course of *H. pylori* infection, this bacteria may disappear from gastric mucosa, and accordingly, patients at more advanced stages of atrophy have a higher risk of developing gastric cancer (*figure 2*).

The acquired evidence on the ABC method has been recently summarized in a book edited by K. Miki [13].

However, there are certain limitations related to the method, see the hints below.

**BOX. Practical hints**

- A positive *H. pylori* serology may be a false-positive in patients with a past infection; most of the recommendations require an additional confirmatory test (such as 13C-urea breath test) to confirm the presence of the infection.
- Prior eradication therapy should be considered when applying the ABC method. Otherwise successful eradication therapy could be the reason for misplacing a patient to a higher risk-group (e.g. from group C to group D).
- It should be mentioned that a significant proportion of subjects (up to 20%) with a positive *H. pylori* serology do not have an active infection even when not self-reporting previous eradication therapy. Therefore, for treatment purposes and to avoid overtreatment, it is recommended that a positive serology be confirmed by an additional test like 13C-urea breath test.

## GASTRIN-17

Recently, an additional marker has been suggested for the characterization of atrophy in the antral part of the stomach – amidated gastrin-17 (G-17) since it is secreted exclusively by the G-cells in this part of the organ [4, 14, 15].

Theoretically, there could be an additional advantage of adding G-17 to the pepsinogen biomarker panel mainly for two reasons: 1) high G-17 and the presence of decreased pepsinogens would confirm the presence of atrophy in the corpus; 2) low G-17 could be indicative of atrophy in the antral part of the stomach.

G-17 levels in the circulation increase after food intake; therefore the measurements of G-17 following a provocation with a protein-rich meal are considered to be the best indicator of antral G-cell function [15, 16]. However, the use of a provocation test is impractical and inconvenient in a screening setting, therefore fasting G-17 is instead being used in many studies [17].

In addition to diet, amidated G-17 levels in the circulation are sensitive to other physiological stimuli, including drug intake (e.g. proton pump inhibitors) [4]. This decreases the value of the test for detecting atrophy in the antral part of the stomach to sensitivity levels far below the acceptable levels for a screening test (15.8% when fasting and 36.8% after stimulation) [18]. No difference in G-17 levels was found between proximally and distally localized gastric cancer [19, 20]. Therefore, currently there seems to be a limited benefit from investigating this parameter.



**Box. Practical hints**

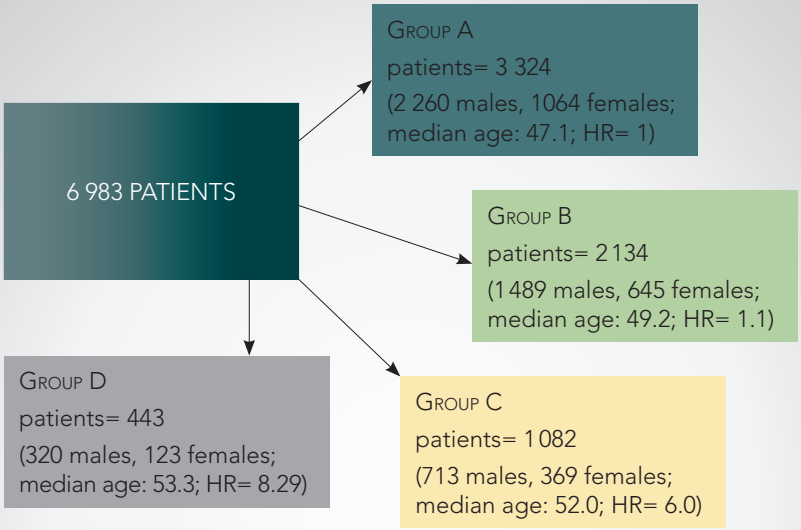
- Amidated gastrin-17 (G-17) can show a compensatory increase under the conditions of corpus atrophy with normal antral mucosa, making it difficult to judge the presence of antral atrophy.
- Although better G-17 results are demonstrated after a food stimulation, performing such a test is not easy in routine practice.

## RECOMMENDATIONS BY THE CURRENT GUIDELINES

Several national, regional and international recommendations and consensus statements have suggested the role of serology in atrophic gastritis and/or gastric cancer risk stratification.

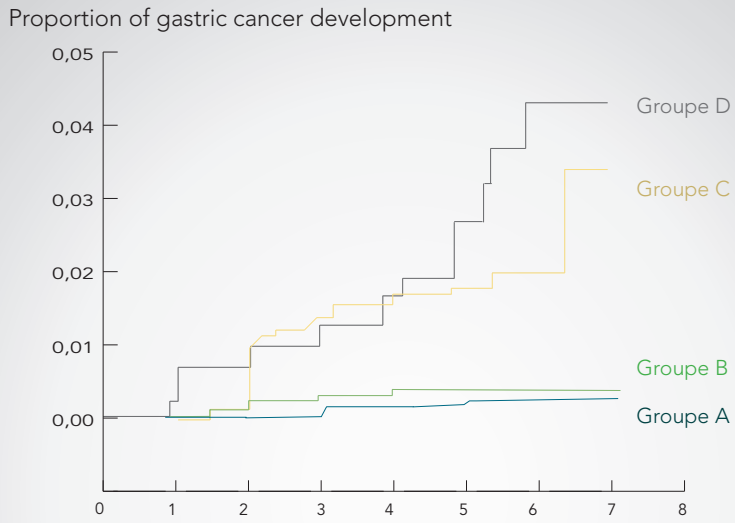
The role of serological tests (pepsinogen I, II, I/II, anti-*H. pylori* antibodies) in gastric cancer risk stratification has been elucidated by the Kyoto Global Consensus (Statement 15; Level of evidence high, Grade of recommendation strong) [21].

Maastricht V/Florence Consensus indicates that the available data consistently recognise pepsinogen serology as the most useful non-invasive test to explore




| | A | B | C | D |
|---|---|---|---|---|
| Pepsinogen index | N | N | ↓ | ↓ |
| IgG anti HP | - | - | + | - |

= SPGI < 70 mg/mL and PGI/PGII ratio < 3.0 ng/mL;
N= all other cases




| | Numbers at risk | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Group A | 3324 | 3217 | 2997 | 2997 | 2734 | 2448 | 1950 | 950 |
| Group B | 2134 | 2071 | 1904 | 1904 | 1726 | 1537 | 1229 | 579 |
| Group C | 1084 | 1050 | 950 | 950 | 866 | 761 | 610 | 298 |
| Group D | 443 | 420 | 384 | 384 | 345 | 305 | 237 | 105 |

Figure 2. Pepsinogen index and gastric cancer cancer risk. * Follow-up average: 4.7 years. SPGI : serum levels of pepsinogens. 12

the status of the gastric mucosa (non-atrophic vs atrophic). The PGI/PGII ratio cannot be considered as a biomarker of gastric neoplasia. (Recommendation 9; Level of evidence 2A, Grade of recommendation A) [8].

MAPS II update is generally in agreement with the above, stating that low pepsinogen I serum levels and/or a low PGI/II ratio can be used to identify patients with advanced stages of atrophic gastritis (Recommendation 11; Quality of evidence moderate, Grade of recommendation strong) [22].

The Brazilian recommendations state that serological analysis of gastric atrophy using pepsinogen I (PGI) and pepsinogen II (PGII), combined with antibodies against *H. pylori* and gastrin-17, can be used to identify populations at risk of gastric cancer (Recommendation 19; Level of evidence 3A, Grade of recommendation B). However, they also state that further studies are necessary to validate this approach in Brazil and other countries of Latin America [23].

Controversially, the British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma do not recommend the use of biomarkers as a screening tool in areas with a low incidence of gastric adenocarcinoma, such as the UK (evidence level: low quality; grade of recommendation: weak; level of agreement: 93%) [24].



## AUTOIMMUNE GASTRITIS: THE RELEVANCE AND SEROLOGICAL METHODS

Patients with autoimmune gastritis (AIG) are reported to have an increased risk of developing gastric cancer. Very recently, in 2020, Weise *et al.* compared a cohort of gastric cancer patients with or without autoimmune gastritis in a case-control study in Germany. They showed that subjects with autoimmune gastritis were detected at earlier stages of cancer which translated into a significantly better 5-year survival [25].

The prevalence of oxyntic gastric atrophy is high in patients with autoimmune thyroid disease, and testing for serum pepsinogens should be included in the clinical assessment of these patients. In 2015, Venerito *et al.* performed a case-control study confirming the accuracy of PGI and PGII for screening of autoimmune gastritis in subjects affected by autoimmune thyroiditis [26].

The presence of antibodies against gastric parietal cells (APCA) that target the α- and β- subunits of the proton pump, have also been suggested as markers for atrophy in the stomach mucosa [17]. APCA is considered to be a marker of autoimmune gastritis. The presence of APCA correlates with atrophy in the corpus part of the stomach [27]; they may precede clinical manifestations of corpus gastritis as pernicious anemia [28].

The intrinsic factor (IF) is a glycoprotein produced by the parietal cells (oxyntic cells) located in the gastric body and fundus [29]. Anti-intrinsic factor antibodies (anti-IFA) have been regarded as a marker of pernicious anaemia and appear at later

stages of atrophic gastritis [4]. Anti-IFA appear to be very specific, but with low sensitivity for the detection of atrophic corpus gastritis.

**Box. Practical hints**

- Both the detection of antibodies against gastric parietal cells (APCA) and anti-intrinsic factor antibodies (anti-IFA) have a place in autoimmune gastritis (AIG) detection, however none of the tests is perfect.
- At this stage, we are still lacking a "gold standard" for serological detection of AIG.

## OTHER EMERGING TESTING MODALITIES

Other promising serological markers for the detection of gastric atrophy exist, such as ghrelin and trefoil factor 3 (TFF3), however they have been less studied.

Ghrelin is a gastric hormone involved in the regulation of hunger and satiety. Ghrelin positive cells can physiologically be detected in all parts of the stomach, but they are mainly distributed in the proximal parts, i.e. the fundus and the proximal corpus region [30, 31]. There is an inverse correlation between ghrelin expression and the degree of inflammation present in the stomach [32]. However, the number of ghrelin positive cells, as well as ghrelin levels in the serum decrease with the progression of preneoplastic and neoplastic alterations of the gastric mucosa [33, 34]. Serum ghrelin is significantly lower in atrophic gastritis compared to early stages of *H. pylori*-induced gastric inflammation. In gastric cancer, ghrelin is almost not expressed at all. Low baseline concentrations of ghrelin in the serum are associated with a higher risk for gastric cancer (OR 1.75; 95% CI 1.49-2.01) [35]. Furthermore, the detected ghrelin levels may depend on preanalytical factors (such as collection and storage of samples).

The TFF family consists of three thermostable and protease-resistant proteins, TFF1, TFF2, and TFF3; these proteins are thought to play a pivotal role in mucosal protection against damage. TFF3 is expressed in goblet cells of the intestine and also at lower levels in other organs, such as the breast, salivary glands, the respiratory tract and the hypothalamus [36].

TFF3 has been suggested as a promising non-invasive biomarker for gastric atrophy and gastric cancer, whether alone or in combination with pepsinogens. A study from China has suggested a better performance of TFF3 (0.81) compared to Pg I/II (0.78) for the detection of corpus atrophic gastritis, and combination of the above may have an even better predictive power [36].

Finally, there are other markers, including micro-RNA panels and volatile markers in the breath that have been studied and demonstrated promising results for the detection of premalignant gastric lesions, including atrophy. However, there is still a long way to go before these biomarkers reach clinical practice.

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# How to recognize and characterize intestinal metaplasia in the stomach at endoscopy

*Should we change our practice ?*

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Gastric cancer is a major health problem worldwide responsible for one third of cancer deaths, and represents the fifth most frequent cancer in terms of incidence. Because most gastric cancers are still diagnosed at symptomatic and advanced stage, their prognosis is poor despite treatment. Therefore, every effort should be made to prevent gastric cancer and to permit earlier detection of the disease at premalignant stages, since patients with chronic atrophic gastritis (AG) or gastric intestinal metaplasia (GIM) are at risk for gastric cancer.

The European Society of Gastrointestinal Endoscopy (ESGE) introduced the first international guidelines on the management of precancerous conditions and lesions of the stomach in 2012, which was updated in 2019 [1]. These guidelines, that are based on new evidence using the Delphi process, provide clear definitions and algorithms to detect and characterize precancerous conditions of the stomach. In fact, gastric carcinogenesis is a multistep process, beginning with AG usually induced by infection with *Helicobacter pylori* (Hp),

which may evolve into GIM, then, to low grade dysplasia, high grade dysplasia, and eventually invasive adenocarcinoma. This "perfect" sequence of events leading to the development of gastric cancer through different steps of precancerous gastric conditions is known as the "Correa's cascade".

GIM can be found in 10-30 % of patients undergoing endoscopy for any indication. Among patients with preneoplastic conditions, GIM is by far the most frequently observed finding (in around 80%) [2]. However, the risk of progression from GIM to gastric cancer is low, and it was estimated to be approximately 3 cases per 1,000 person-years in a recent meta-analysis [3]. In contrast, the risk of progression from GIM to dysplasia is slightly higher, at around 12 cases per 1,000 person-years. This risk may be higher in patients with incomplete and/or extensive GIM [4, 5].

For these reasons, a precise risk stratification for gastric cancer encompasses not only the endoscopic identification but also the extension of preneoplastic changes. It is therefore crucial for endoscopists to be aware of the different patterns that gastric mucosa may exhibit in the presence of AG or GIM. It is important to bear in mind that most of the preneoplastic conditions are found in the antrum, followed by the corpus and a pangastric location, not only in western countries but also in other populations [4]. Combining better knowledge of gastric patterns with advanced endoscopy and the multistep process of carcinogenesis should therefore help in the detection and treatment of patients at an earlier stage.



## WHITE LIGHT ENDOSCOPY DETECTION OF GASTRIC INTESTINAL METAPLASIA

White light endoscopy (WLE) remains the first step for endoscopic examination because of the additional information that it provides for diagnosis, namely for the detection of gastric lesions and prediction of deep submucosal invasion [6]. Similarly, different findings related to the presence of GIM have been described over the years. Initially, GIM was described as whitish, flat or slightly elevated areas (*figure 1*) [7]. Later, a different pattern named "mottled patchy erythema" was reported, which are depressed reddish areas [8]. Nevertheless, the colour of GIM under WLE can also be similar to the surrounding mucosa [6], so the diagnosis of GIM under WLE can be challenging since it can show subtle changes.

Results from studies addressing conventional WLE for GIM detection, showed a poor correlation between endoscopic findings and histological diagnosis [9]. Despite the improvements of diagnostic accuracy with the introduction of high-definition (HD)-WLE, its sensitivity and interobserver agreement still remain low [10-12].

High magnification HD-WLE may improve the endoscopic accuracy because of its ability to characterize microsurface patterns. Gastric mucosa of normal antrum shows a groove-type structure and normal corpus has a foveolar-type appearance. However, in the presence of GIM, the microsurface appearance changes to groove-type or villiform structures, mimicking the normal antral or intestinal mucosa [6]. High magnification can be useful for the characterization of the microsurface pattern but it is still unavailable in several endoscopic units worldwide. Moreover, there is scarce data regarding its real impact in terms of diagnostic accuracy for GIM detection [13].

Accordingly, the diagnosis of GIM under WLE remains unsatisfactory, and the diagnostic accuracy relies mostly on the endoscopist´s experience, but even in those situations, biopsies are still necessary.

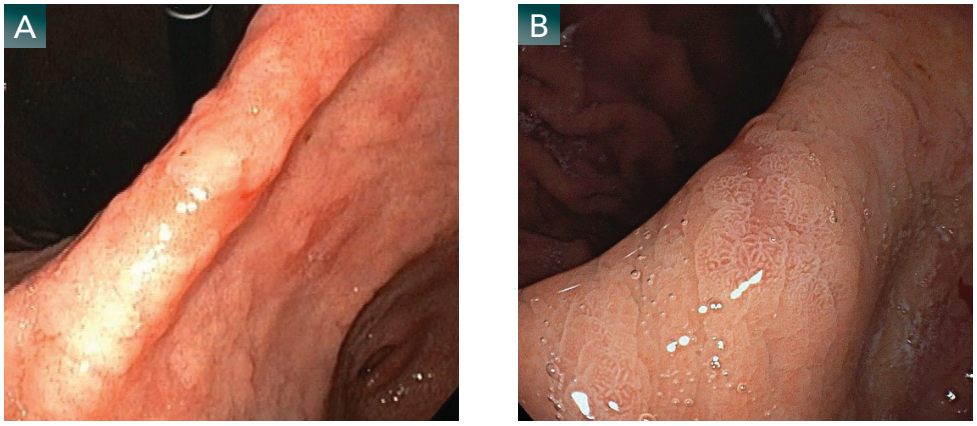


FIGURE 1. Examples of gastric intestinal metaplasia under white light endoscopy. Whitish elevated areas (a) showing tubulovillous pattern (b) can be seen in the incisura.



## CHROMOENDOSCOPY DETECTION AND STAGING OF GASTRIC INTESTINAL METAPLASIA

In order to increase the diagnostic accuracy of gastrointestinal endoscopy, new techniques have been developed in the past few years. Among them, image-enhanced endoscopy is an emerging technique, which comprises two modalities, conventional chromoendoscopy and virtual chromoendoscopy (divided into optical-digital, and digital according to the enhancement image processing). Conventional chromoendoscopy improves the contrast of the mucosa by applying different kinds of dyes, and its use showed an increase in overall accuracy for the diagnosis of preneoplastic conditions [14]. However, it has not been universally adopted because it is a cumbersome technique. Converse-

ly, virtual chromoendoscopy has the additional advantage of simplicity of use ("push-button technology") and higher image quality.

Previous studies reported different endoscopic descriptors for GIM according to the type of image-enhanced endoscopy technology, with narrow-band imaging (NBI) being the most evaluated. With this technology, the two most assessed markers were the presence of bluish-whitish patches [15] and areas with a tubulovillous pattern [16] (*figure 2*). With NBI under high magnification (ME-NBI), a fine blue-white line can be present on the crests of the epithelial surface or gyri, named light blue crest (LBC) [17].

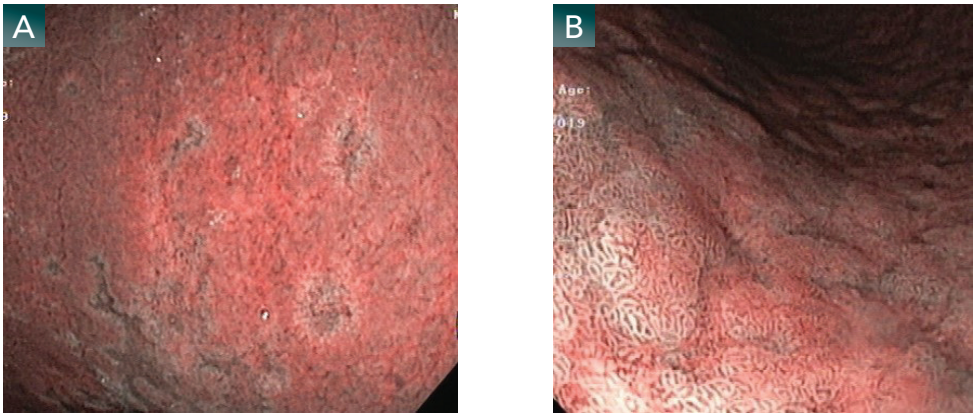


FIGURE 2. Examples of gastric intestinal metaplasia under narrow-band imaging. Slightly elevated areas showing tubulovillous pattern can be seen in the lesser curvature of the corpus (a) and the greater curvature of the antrum (b).

The high diagnostic yield of NBI and ME-NBI for the diagnosis of GIM have been reported in several studies, showing an accuracy of over 90% [10, 11]. However, slight differences have been observed according to the type of endoscopic marker evaluated. Without high magnification, tubulovillous pattern was demonstrated to be highly accurate and reproducible [10, 16], and under ME-NBI, the presence of LBC demonstrated high performance [17]. Nevertheless, discrepancies in LBC definition have been noticed which may influence its reproducibility [18]. A recent meta-analysis assessing different image-enhanced endoscopy technologies and endoscopic markers obtained the best results with tubulovillous pattern, even without using high magnification (sensitivity of 88%, specificity 97%) [18]. As a result, tubulovillous pattern has been suggested as the most reliable marker for the detection of GIM.

Despite the fact that NBI has been the most validated technology for the diagnosis of GIM, the accuracy of other image-enhanced endoscopy technologies has also been evaluated. With autofluorescence imaging (AFI), antrum GIM appears as multiple purplish areas on a green background, and fundic GIM as homogeneous green

areas on a purple background. In spite of the additional value of AFI over WLE, specificity of AFI is still low [19], for this reason, the use of AFI as a "red flag" tool followed by ME-NBI was proposed, which is known as trimodal imaging (TMI). However, although TMI seems to substantially improve the diagnosis of dysplastic lesions, its specificity for preneoplastic conditions remains low [20]. Fewer studies have addressed the performance of flexible spectral imaging color enhancement (FICE), and the most evaluated markers were LBC, tubulovillous pattern and large long crest (a combination of linear dark and light areas that differed from the normal gastric epithelium). However, this image-enhanced endoscopy technology also seems to be suboptimal for GIM identification, only improved by its combination with high magnification and/or probe-based confocal laser endomicroscopy (pCLE) [21]. Better results have been recently reported regarding linked colour imaging (LCI) and blue laser imaging/blue light imaging (BLI). With LCI, GIM has been described as lavender colour areas ("lavender colour sign"), and its high accuracy has been recently reported [22]. Nonetheless, the most promising results have been obtained with BLI. Owing to the similarities between NBI and BLI (both technologies are based on the same physical principle), the images produced are similar. Consequently, the same endoscopic markers for GIM with BLI and NBI have been considered (*figure 3*). One study evaluating blue laser imaging under high magnification obtained an accuracy of 94%, which is comparable to that previously reported with ME-NBI [23]. The recent multi-LED technology (BLI) has also been evaluated in a prospective study, and despite the small cohort, it demonstrated a high accuracy for advanced stages of GIM as well as interobserver agreement [24]. Although more studies are necessary to reach consistent conclusions, it is expected that NBI and BLI will be equally effective.



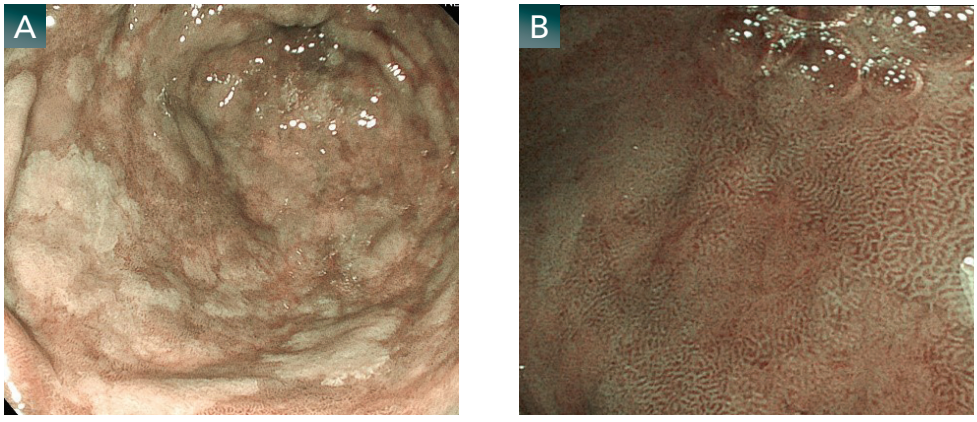


FIGURE 3. Examples of gastric intestinal metaplasia. The presence of slightly elevated bluish-whitish areas (a) showing tubulovillous pattern (b) can be seen in the antrum under blue light imaging, with and without bright mode, respectively.

HOW TO RECOGNIZE AND CHARACTERIZE INTESTINAL DYSPLASIA IN THE STOMACH





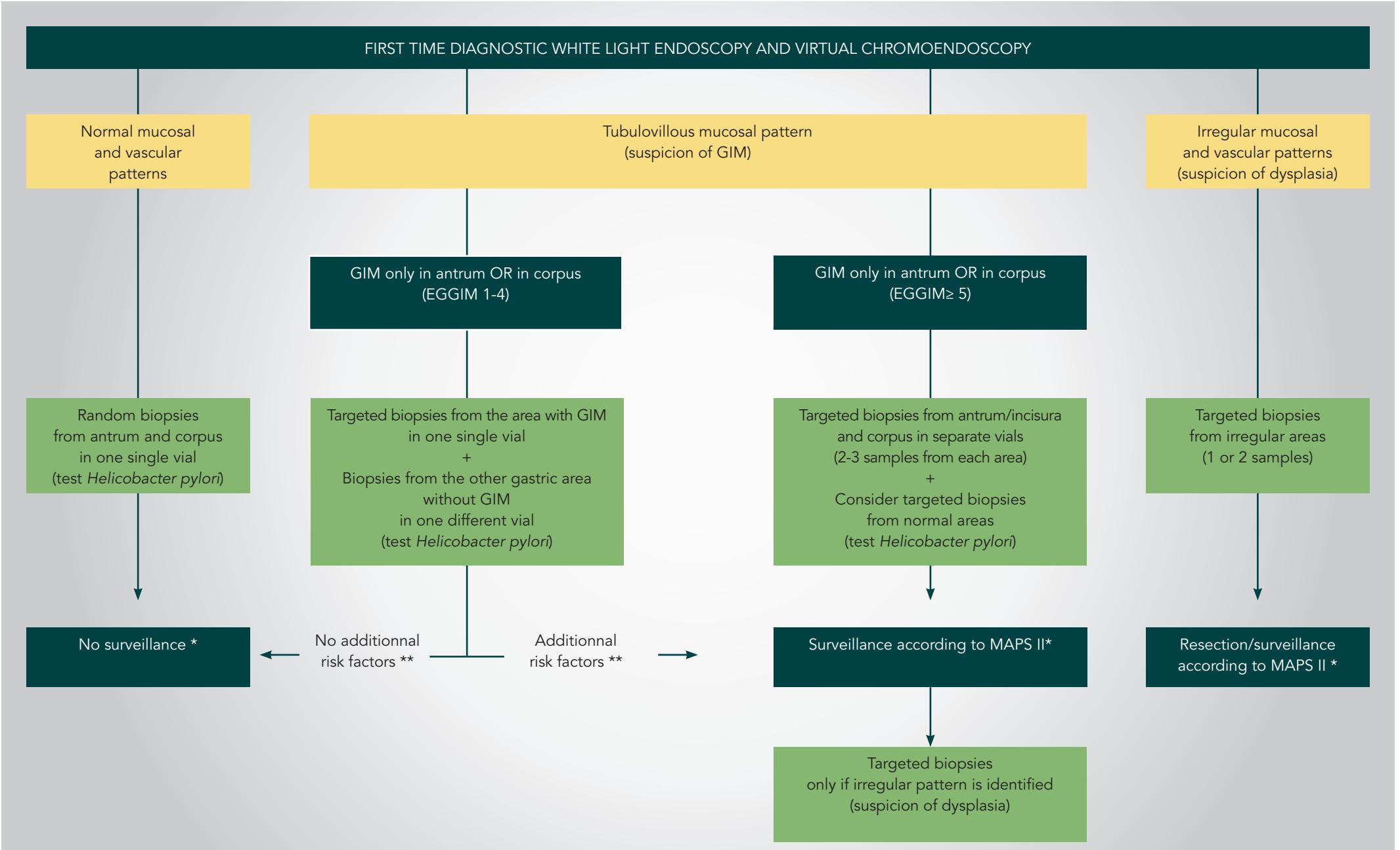


FIGURE 4. Suggested endoscopic approach for the detection and follow-up of gastric intestinal metaplasia (GIM). * Eradication of *Helicobacter pylori* if positive; ** family history of gastric cancer, incomplete type GIM, autoimmune gastritis, or persistent *Helicobacter pylori* infection. MAPS: MAnagement of epithelial Precancerous conditions and lesions in the Stomach.



Rodriguez-Carrasco M, Coron E, Dinis-Ribeiro M, Pimentel-Nunes P

## SHOULD WE CHANGE OUR PRACTICE?

The benefits of image-enhanced endoscopy technologies vs. HD-WLE for the detection of GIM seem obvious, but histological confirmation is still necessary. Accordingly, current ESGE guidelines recommend guiding biopsies by virtual chromoendoscopy [1]. One of the reasons to challenge the benefit of targeted biopsies instead of mapping (according to updated Sidney protocol), is the fact that the patchy and multifocal presentation of GIM can affect the detection rate. In this context, two comparative studies of the two strategies concluded that they are complementary as their combination achieved the best detection rate of GIM [25, 26]. One of the studies added that a high proportion of missed NBI cases (48%) corresponded to mild GIM [26]. Although NBI will probably have a limited ability to detect focal and mild GIM, the clinical impact does not seem to be significant, as those cases will not benefit from endoscopic surveillance.



Altogether, these results led to a new approach for endoscopic staging of GIM and a new NBI staging classification has been proposed, the Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) [10]. The main advantage of this classification is the possibility to endoscopically assess the entire gastric mucosa instead of the histological assessment of tiny areas. Furthermore, it was recently validated in a multicentre study, and it was demonstrated that with EGGIM of between 5-10, the sensitivity and specificity to detect extensive stages of GIM (OLGIM III/IV) were 89% and 95%, respectively [27]. Moreover, in a recently published study EGGIM was shown to be strongly correlated to gastric cancer risk even without biopsies, validating this tool as an independent risk factor for gastric cancer [28].

Accordingly, a new strategy to detect and stage GIM has been proposed [29]. This approach focusses on the importance of a high-quality examination to obtain a more accurate diagnosis, and optimize the biopsy protocol instead of relying only on random biopsies. The decision to perform targeted biopsies by NBI should be based on different clinical scenarios which includes the findings at initial endoscopy along with personal risk factors for gastric cancer (*figure 4*). The first scenario would involve the detection of a normal mucosa under WLE and EGGIM 0 under NBI. Considering the excellent negative predictive value of NBI for detecting advanced stages of GIM, biopsies performed according to the updated Sydney System but put in one single vial are enough to confirm endoscopic diagnosis (absence of GIM) and to check for *H. pylori* infection [30]. The second scenario would involve the detection of AG under WLE and/or EGGIM 1-4 observed under NBI. In these situations, the possible risk of under- or overestimation of gastritis makes it difficult to rely solely on endoscopic

diagnosis. Targeted biopsies should be taken from GIM areas, as well as from normal areas (in separate vials according to the gastric area), so OLGIM stage can be confirmed and *H. pylori* tested. The third scenario would involve the detection of extensive GIM. Targeted biopsies in at least 2 separate vials (antrum and corpus) should be taken to confirm the diagnosis, as well as from normal areas in case of *H. pylori* testing. In contrast, endoscopic surveillance biopsies would not be necessary unless an area suspicious for dysplasia is seen (targeted biopsy, 1 or 2 fragments) or if we want to check the *H. pylori* status (in this case, biopsies should be taken from the normal mucosa, most commonly colonized by this bacterium).

## CONCLUSION

The benefits of virtual chromoendoscopy over WLE for the diagnosis of GIM have been demonstrated in numerous studies, and NBI seems to be the most accurate technology for this purpose. Although different endoscopic markers have been evaluated, the presence of the tubulovillous pattern is probably the most reliable marker for the identification of GIM areas. The improvements in endoscopic imaging is changing the diagnostic approach, grading and follow-up of patients with different stages of GIM. This new approach allows endoscopists to increasingly rely on endoscopic imaging and consider biopsies as a complementary and still necessary part on the diagnostic process, but not the fundamental one.



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# Management of gastric premalignant lesions

## What should clinicians do today?

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Gastric precancerous lesions (GPL), which include chronic atrophic gastritis, gastric intestinal metaplasia (IM), and dysplasia, are associated with an increased risk of gastric cancer (GC) [1]. This risk depends on the type of the lesion (lower for atrophic gastritis, higher for IM and the highest for dysplasia), the severity of the lesions expressed by different histopathological scores (OLGA for atrophic gastritis, OLGIM for IM, and low or high grade for dysplasia), the extension of the lesions within the stomach (focal or patchy distribution, exclusive antrum or corpus involvement, or extended pangastritis), and on some specific characteristics of the lesions like the type of IM (complete or incomplete) [1-6].

A detailed histological description of the different types and stages of GPL is provided in another chapter of this book, but here it is important to underline that specific anatomical and histological patterns of GPL confer, together with other factors, a specific risk of evolution to GC and therefore should be evaluated and taken into account while considering the surveillance modalities [7–9].

Given an increased risk of GC in patients with GPL, the surveillance of these patients seems to be a logical approach to prevent the risk of advanced GC. This approach has shown its efficacy in countries with a high risk of incidence of GC, like some Asian countries [10-13], and it has also been tested in Europe [1,14].

In Singapore, endoscopic surveillance of patients with GPL has been shown to be efficient and cost-effective with a recommended surveillance interval of 1 to 2 years [15,16]. In Portugal, a country considered as intermediate GC incidence area, the systematic endoscopic surveillance of patients with GPL has also been shown to be cost-effective with a proposed surveillance interval of every 3 years [17].

Although most European countries are classified as low or intermediate GC risk areas, it is now considered that surveillance of patients with GPL is indicat-

ed and several European guidelines on the management of patients with these lesions have been published in the past few years [18-21]. (*figure 1*).

Other guidelines have also been elaborated, and in particular by the American Gastroenterology Association (AGA Guidelines, [22]), as well as by the Chilean Association for Digestive Endoscopy [23].

There are differences among these guidelines, some of them specifically addressing particular aspects, like the surveillance of gastric IM only in the AGA guidelines, and some covering the entire spectrum of the different aspects of histological diagnosis, surveillance and treatment of patients with all types of GPL. There are also some differences in the recommendations proposed, in particular with respect to the surveillance, reflecting the differences in the epidemiological context and healthcare systems in different countries. However, despite these differences, there are two common points highlighted by all of the guidelines:

1. The necessity to search for *Helicobacter pylori* (*H. pylori)* infection in all patients with GPL and eradicate this infection if present.
2. The indication of stratifying the risk according to the histological results (severity and extension of gastric atrophy and IM), as well as other factors like persistent *H. pylori* infection, family history of GC, or ethnic origin of the patient.



In Europe, in addition to some national guidelines [20,21], international European guidelines have been published (so called "MAPS" guidelines, for Management of precancerous conditions and lesions in the stomach), elaborated by several European Societies, with participation of experts representing the majority of European countries, and thus globally adapted to the European context. The first version of these guidelines was published in 2012 [18] and more recently, a new, updated version was published, integrating the recent advances in our knowledge on diagnosis and evolution of GPL, as well as the progress in endoscopy (MAPS II, [19])

The recommendations given below are mainly based on the MAPS guidelines, but a referral to other guidelines is made as well.

## INITIAL DIAGNOSIS AND "STAGING" OF GPL

### Endoscopy

The importance of a good quality endoscopic assessment is underlined. This aspect is addressed in more detail in a dedicated chapter of this book. In general, endoscopic evaluation should be performed using high-resolution endoscopy and whenever possible with chromoendoscopy (virtual or dye-based), which is superior to standard endoscopy and allows for a better evaluation of the gastric mucosa and identification of areas suspected of atrophy or IM, thus allowing the implementation of targeted rather than random biopsies.

Performing biopsies is necessary, and at least 4 biopsies (2 from the antrum and 2 from the corpus), and if possible an additional biopsy from the incisura, should be obtained and placed into two separate vials (from the antrum and incisura in one vial, and from the corpus in the second vial).

In case of an initial diagnosis made "accidentally", on the basis of histological analysis of a gastric biopsy obtained for other reasons and without a correct endoscopic protocol, a second endoscopy should be proposed within a short interval period (<6 months) in order to obtain a correct endoscopic and histological evaluation. This recommendation is included in the British guidelines, and although it is not explicitly stated in the MAPS guidelines, it seems logical since it is clearly indicated that a correct endoscopic evaluation and histological analysis of at least 4 biopsies, from the antrum and from the corpus, are necessary, which is usually not the case during an average endoscopic procedure.

## Histology

The histological evaluation is described in detail in the dedicated chapter. It should be preferentially performed by a Pathologist who has experience in gastric pathology. It should include the evaluation of the type and severity of the lesions according to the OLGA and OLGIM score, and, if possible, the evaluation of the type of IM (complete or incomplete type).



## Non-invasive markers of gastric atrophy

All guidelines recognize the usefulness of measuring serum pepsinogen (PG) I and II, which allows for a global evaluation of the state of the gastric mucosa, and in particular of its secretory capacities, which are impaired in case of gastric atrophy. Indeed, in case of marked destruction of the gastric glands, there is an impairment of pepsinogen secretion, and in particular decreased levels of PGI and decreased PGI/PGII ratio are observed.

Although this dosage is not performed routinely, and is not reimbursed in the majority of European countries, it could be recommended whenever possible. If it cannot be currently performed, it is recommended to obtain a blood sample from the patient and store the serum frozen for a potential future analysis.

## *Helicobacter pylori*

The search for *H. pylori* infection is mandatory, and should be performed in all patients with GPL and in case of a positive test, the bacteria should be eradicated [24-26].

The positive effect of *H. pylori* eradication on the evolution of GPL is reflected by several findings: 1) *H. pylori* eradication reduces inflammation, it may reverse the atrophy and in some cases even IM [27], 2) *H. pylori* eradication after endoscopic resection of early gastric cancer (usually associated with pre-existing

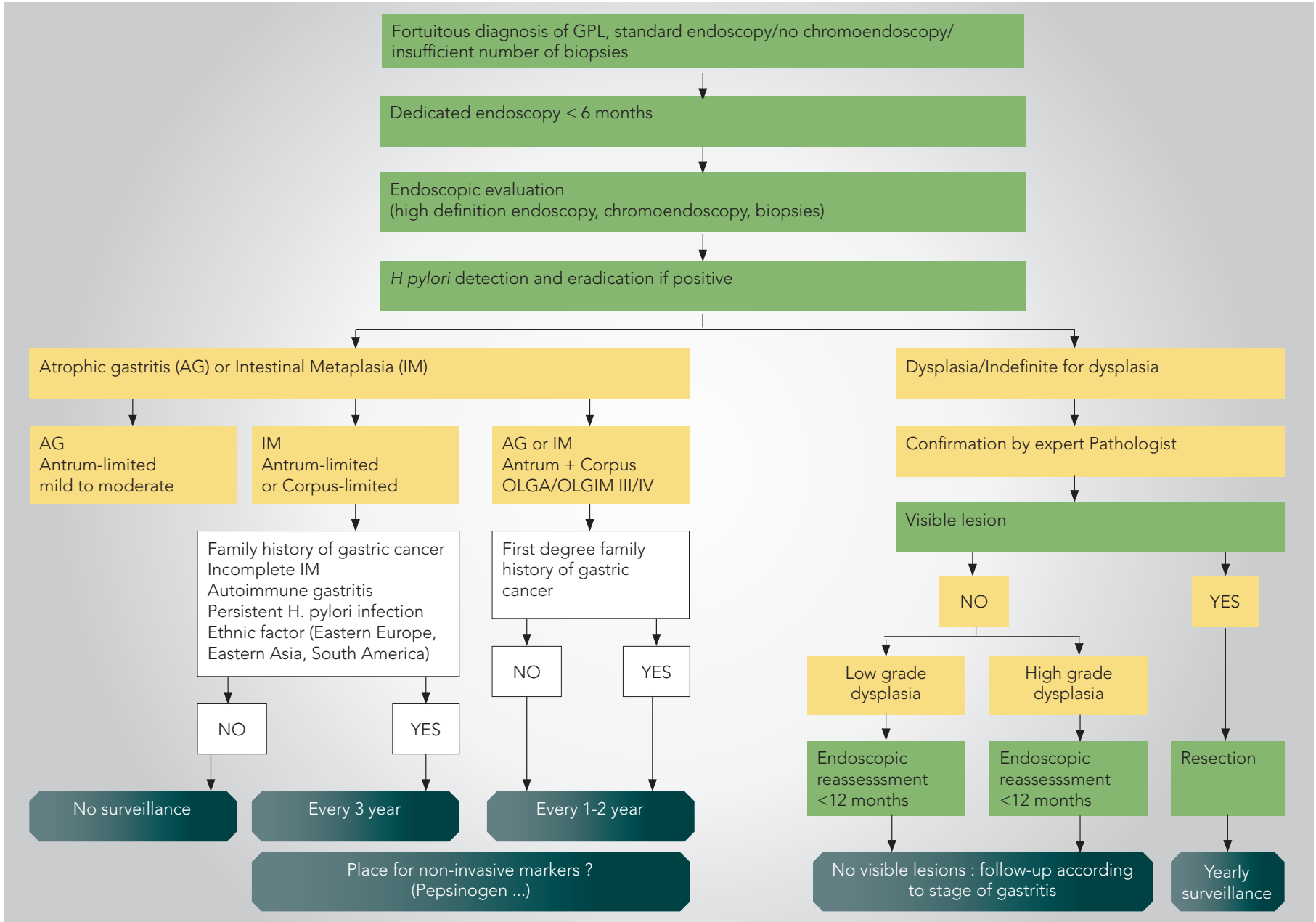


FIGURE 1. Algorithm for the surveillance of patients with Gastric precancerous lesions (GPL) adapted from Pimentel Nunes *et al* 19. AG: Atrophic Gastritis, OLGA: Operative Link on Gastritis Assessment, OLGIM: Operative Link on Gastritis Assessment based on Intestinal Metaplasia ; IM: Intestinal Metaplasia.



MANAGEMENT OF GASTRIC PREMALIGNANT LESIONS



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GPL) leads to a significant decrease in the risk of metachronous GC [28], 3) *H. pylori* eradication leads to a significant decrease in GPL prevalence, as well as GC incidence and mortality at a population-level [29].

The bacterium can be detected by histology, but in case of negative histology, serology should be performed to confirm the absence of the bacteria. Indeed, in case of gastric atrophy, the sensitivity of biopsy-based methods, as well as the urea-breath test, is decreased, and serology seems to be the most sensitive method, the only one not affected by the status of the gastric mucosa, and therefore recommended in this setting.

The eradication regimen should be preferably proposed according to the results of antimicrobial susceptibility testing, performed either by real-time PCR directly on gastric biopsies (for clarithromycin), or by classical antibiogram after bacterial culture (for all antibiotics). If pre-treatment testing is not possible, the empirical treatment should be applied according to validated local recommendations.

### Family history



Family history is important, and in particular the history of GC, as well as information on the ethnic origin of the patients, and this information should be recorded. Indeed, even when living in low incidence countries, individuals originating from high GC incidence area, like Asian or South American countries, are considered to be at an increased risk of GC [30,31]. However, whether the ethnic factor confers an independent increased risk of evolution from GPL to GC remains still unproven.

## SURVEILLANCE OF GPL

### Dysplasia

Among all GPL, dysplasia, and in particular high grade dysplasia, is associated with the highest risk of evolution to GC with an annual rate of 6% [1], and it is estimated that one out of 19 patients with dysplasia will develop GC within 20 years [3]. In case of dysplasia, found on the gastric mucosa without an endoscopically defined lesion, an immediate high quality endoscopic reassessment with chromoendoscopy and multiple gastric biopsies should be performed. Although the exact number of biopsies is not specified, it can be reasonably proposed that at least 3 biopsies from the antrum, 3 from the corpus and 2 biopsies from the incisura region should be obtained. If the histopathological analysis confirms a high-grade dysplasia, the control endoscopy with multiple biopsies should be performed within 6 months, while in case of low grade dysplasia, within 12 months.

## Intestinal metaplasia

Intestinal metaplasia confers an intermediate risk of evolution to GC, evaluated at 0.25% per year [1], and it is estimated that one out of 39 patients will develop GC within 20 years [3]. This risk may vary depending on the severity and extension of the lesions, as well as according to the type of IM (complete or incomplete). It is now well established, that patients with extended IM and incomplete IM, have a higher risk of GC. However, some studies suggest that even IM limited to the antrum may confer an increased risk of GC if the incomplete type is present [32].

In case of IM at a single location (limited to the antrum or the corpus), without severe atrophy and without any other particular risk factors, no systematic surveillance is indicated. However, this surveillance should be proposed in case of incomplete type of IM, family history of GC, or persistent *H. pylori* infection with a control endoscopy with guided biopsies every 3 years.

In case of IM extended to both the antrum and the corpus (score OLGIM III/IV), independently of the existence of other risk factors, endoscopic surveillance should be proposed every 3 years. In the presence of additional risk factors (advanced atrophy, family history of GC, incomplete type of IM), stricter surveillance should be proposed (surveillance endoscopy every 1 to 2 years).



## Atrophic gastritis

Patients with chronic atrophic gastritis have a higher risk of GC compared to the general population, with the annual risk varying from 0.1 to 0.25% in different studies [1,21]. This risk depends on the severity and extension of gastric atrophy. In case of mild or moderate gastric atrophy restricted to the antrum, without IM, there is no evidence to support the recommendation of surveillance endoscopy.

In case of advanced atrophic gastritis with severe atrophic changes extended to both the antrum and the corpus (OLGA III/IV), associated or not with IM, endoscopic surveillance every 3 years is recommended. In the presence of additional risk factors, like family history of GC, these patients may benefit from stricter surveillance (every 1 to 2 years).

Patients with autoimmune gastritis may also benefit from endoscopic surveillance every 3 to 5 years. We should keep in mind that in these patients, the risk of developing neuroendocrine tumors greatly outweighs the risk of developing adenocarcinoma.

# FUTURE DIRECTIONS

In the future, better stratification of patients with GPL according to their individual risk of evolution to GC will allow for the application of more efficient and cost-effective surveillance strategies. Better assessment of the individual risk level will be achieved thanks to the progress in endoscopic techniques, blood

markers as well as molecular markers, currently under study 33-35. The appropriate organization of the detection/surveillance health system adapted to the local context will also be helpful [1].

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# Endoscopic treatment of early gastric cancer

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Gastric cancer is one of the most common and lethal malignancies worldwide, with over a million incident cases and accounting for 8% of all cancer deaths in 2018 [1,2]. While traditionally diagnosed at advanced stages, especially in the West, the more widespread use of upper endoscopy has increased the detection of early gastric neoplasms. These are defined as adenocarcinoma restricted to the mucosa or submucosa, irrespective of lymph node status (i.e. T1, any N). [3]

Gastrectomy with lymphadenectomy was the standard treatment for gastric cancer. However, early gastric cancer has a low probability of lymph node spread and may be appropriately treated with endoscopic resection. Based on surgical series of pT1 gastric cancers, factors associated with higher risk of lymph node involvement include larger lesion size, ulceration, undifferentiated histology, depth of invasion and lymphovascular or perineural invasion [4]. After endoscopic resection, histopathological evaluation of the lesion must assess these features in order to define the likelihood of an endoscopic cure; in lesions with high-risk criteria, gastrectomy and lymphadenectomy should be considered.

In this chapter we review the different techniques for endoscopic resection of early gastric cancer, discuss the pre-treatment lesion evaluation and the post-resection histological assessment and follow-up. An algorithm for the management of early gastric neoplasms is proposed in *figure 1*.

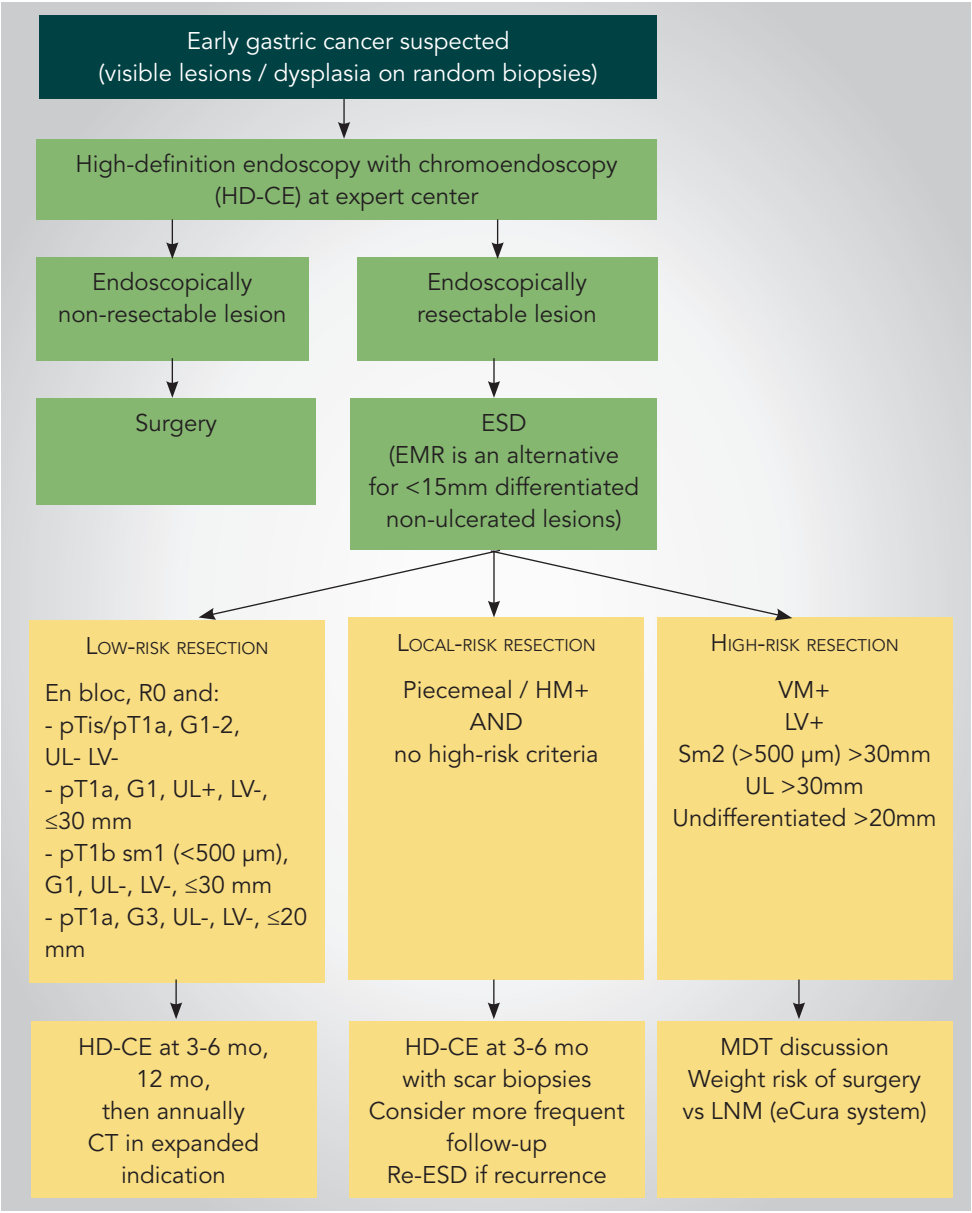



FIGURE 1. Algorithm for early gastric cancer management. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection (G1-2, well/moderately differentiated lesions; G3, undifferentiated lesion); HM, horizontal margin; LV, lymphovascular invasion; LNM, lymph node metastasis; MDT, multidisciplinary team; mo, months; R0, free margin resection; UL, ulceration; VM, vertical margin.

## PRE-TREATMENT LESION EVALUATION

When an early gastric neoplasm is suspected (either as a visible lesion or as neoplasia in random biopsies), endoscopy is the most informative diagnostic and staging procedure. This endoscopic assessment is important to detect previously unrecognized lesions (including synchronous neoplasms) and to predict the resectability and curability of the lesion, allowing a more informed decision on the best treatment option for each individual lesion and patient.

Early gastric cancer can present as a polypoid protrusion, slightly raised plaque, mucosal discoloration, depression, erosion or an ulcer; subtle, small and flat lesions may be missed by endoscopy. In fact, high-definition white-light endoscopy (WLE) shows poor to modest sensitivity in the detection of early gastric cancer [5,6] and the miss-rate for upper gastrointestinal cancers can be as high as 11% [7]. This may be due to inadequate inspection, failure to recognize a lesion, sampling error or pathologist error. However, a careful endoscopic observation paired with chromoendoscopy by an experienced user can increase early gastric cancer detection [6,8,9] and should be offered after any diagnosis of gastric neoplasia, even if no lesion was described.



Endoscopic evaluation can predict the T stage (including distinction between T1a and T1b) with 78% accuracy [10]. Lesion size, location and morphology are predictors of resectability and curability and should be carefully assessed [11]. Lesion morphology should be described using the Paris classification and other features associated with submucosal invasion should be noted: irregular/nodular surface protrusion, irregular depression, and clubbing, fusion or abrupt cutting of convergent folds. In contrast, mucosal lesions more often show smooth protrusion, shallow and even depression, flat/superficial spread, and erosion with slightly raised margins [10]. Dye-based or digital chromoendoscopy should ideally be employed to improve diagnosis, staging and margin delineation, as they have been associated with improved detection of lesions and diagnosis of dysplasia compared to WLE. [6]

Although abdominal CT is part of gastric cancer staging, early neoplastic lesions for which endoscopic resection is considered have a very low risk of lymph node metastasis. In this situation, CT is not deemed mandatory, as it is more likely to show benign findings which may lead to unfounded doubts regarding endoscopic resection. In the West, endoscopic ultrasonography (EUS) is usually recommended before endoscopic resection, as it is believed to be the most accurate method for T staging. However, the use of EUS to determine the resectability of a lesion is controversial. Its accuracy is lower for early gastric cancer stages (T1-T2) [12,13] and in one comparative study resulted in a high rate of over-staging when compared to endoscopic evaluation [10]. Moreover, if endoscopic resection is deemed feasible, histological specimen analysis represents the most accurate staging method and

does not preclude subsequent surgery if a higher risk lesion is found. Accordingly, European guidelines suggest that an expert endoscopic assessment is enough to determine the feasibility of endoscopic resection in the majority of lesions, with further staging procedures reserved for selected cases [14].

## ENDOSCOPIC RESECTION

Endoscopic mucosal resection (EMR) was the first endoscopic alternative to gastrectomy for the treatment of early gastric cancer, with early Asian series reporting disease-specific survival of 99% at 5 and 10 years after a complete en bloc resection of select small mucosal lesions [15]. Subsequent Western series also reported high rates (97%) of long-term remission after EMR of small (<30 mm), intramucosal, differentiated tumors without lymphovascular invasion; however, these results were limited by low en bloc and R0 resections and high recurrence rates (up to 30%) [16]. Several EMR techniques have been described, namely injection-, cap- or band-assisted EMR (*figure 2*); however, all are limited by the size of the snare in terms of en bloc resection.



Endoscopic submucosal dissection (ESD) was developed in Japan to allow en bloc resection of gastric lesions regardless of size *(figure 3)* [17]. Several meta-analyses comparing both techniques demonstrated higher en bloc and R0 resection rates for ESD, with lower resection rates and similar post-procedural bleeding. These advantages are maintained even in lesions <10mm, but are counterbalanced by longer procedure times and a higher perforation risk [18-23]. Many recent Western series have replicated the earlier good outcomes reported in the East, with >90% of en bloc and complete resections, 70-80% curative resection rates, local recurrence of <5% and acceptable adverse event rates (post-procedural bleeding in 5-10% and perforation in <3%) [24-27].

When compared with gastrectomy in meta-analyses, ESD shows significantly lower procedural time, length of hospital stay, adverse event rates and procedure-related mortality. Overall and disease-specific survival rates are comparable (>95% and >99%, respectively), although recurrence and metachronous lesions are more common after ESD (2 vs 0.2% and 7 vs 0.4%, respectively) [28–31]. ESD is also associated with a better quality of life at 1 year when compared with gastrectomy [26].

Based on this evidence, European guidelines recommend ESD as the first-line endoscopic procedure for early gastric cancer treatment, with EMR being an alternative for small (<15 mm) elevated lesions in which en bloc R0 resection is deemed likely [14]. Nevertheless, the pros and cons of endoscopic resection versus surgical treatment should always be disclosed to the patient, especially the risk of non-curative (i.e. high risk of lymph node metastasis [LNM]) resection even after successful endoscopic excision.

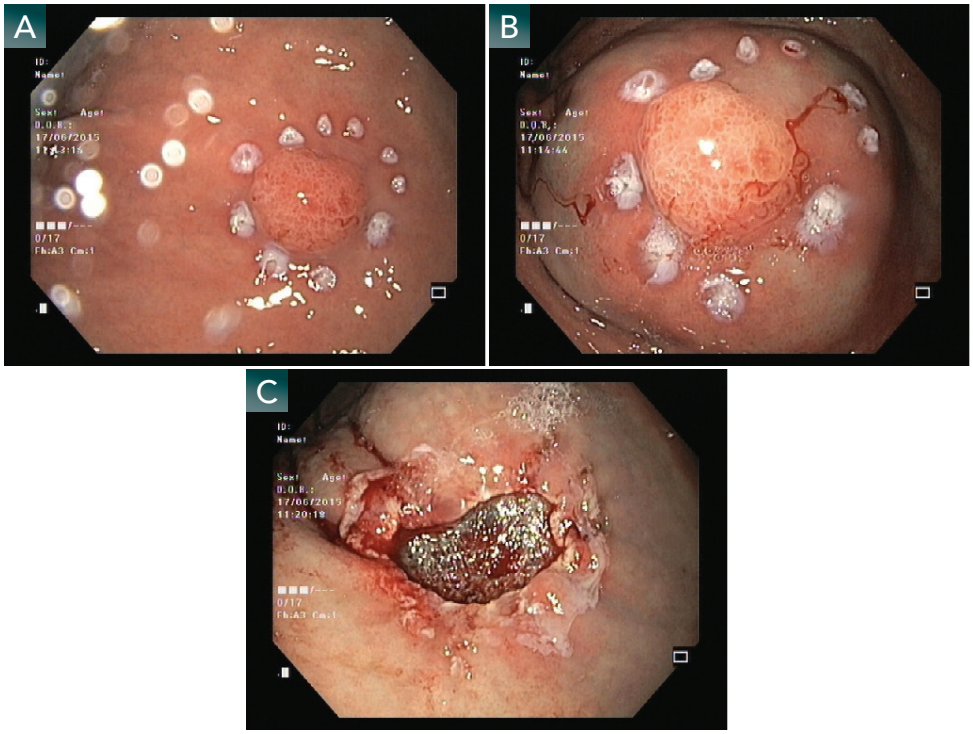
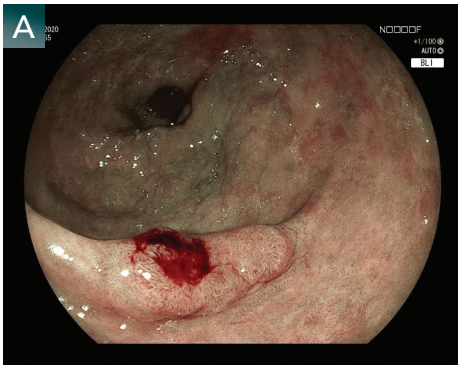



FIGURE 2. Gastric cap-assisted endoscopic mucosal resection (in this case, of a grade 1 neuroendocrine tumor). A) Lesion delineation using coagulation current; B) the endoscope is removed and the cap is fitted onto its tip. After submucosal injection, the snare is positioned into the cap loop and the lesion aspirated into the cap. All the margin marks should be visible inside the cap; C) the snare is closed around the lesion and blended current is used to resect the lesion.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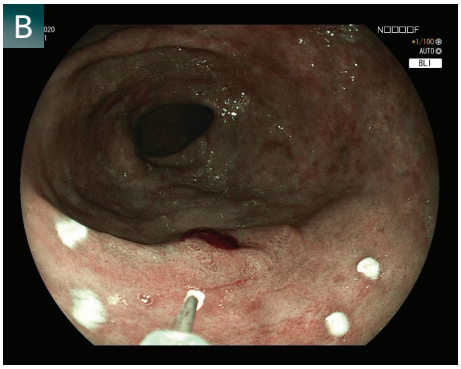
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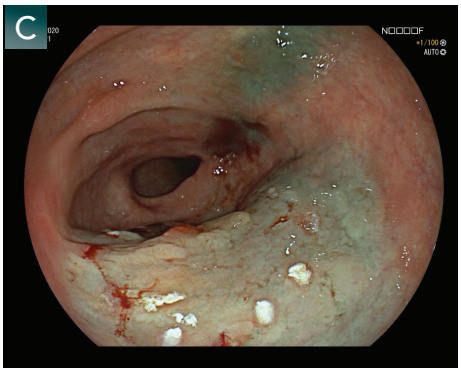
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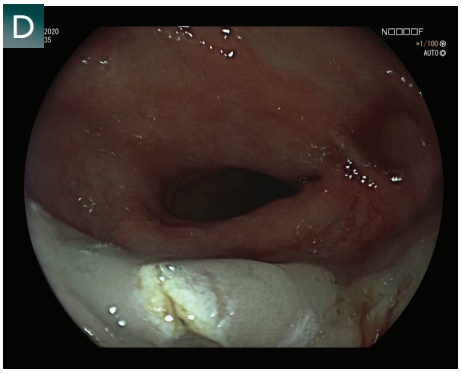
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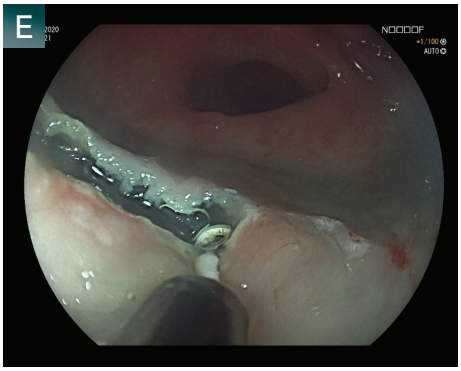
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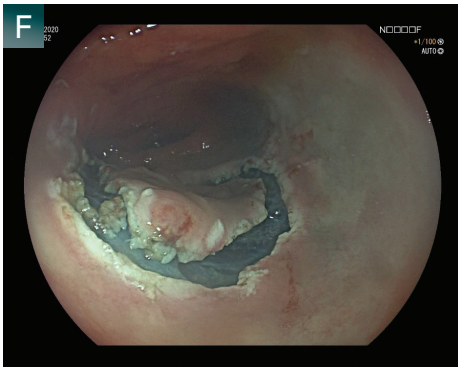
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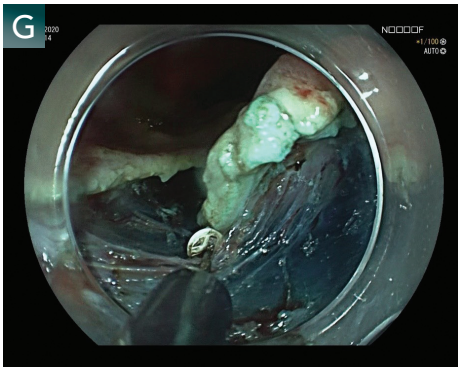


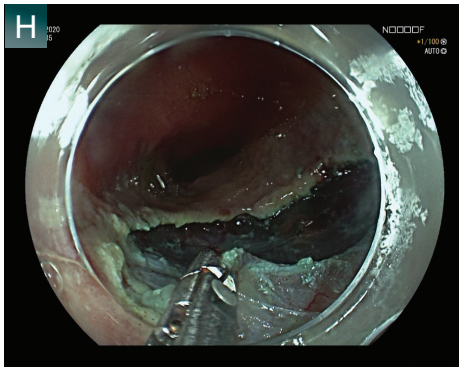




FIGURE 3. Endoscopic submucosal dissection technique. A) Prior to resection, careful lesion inspection to assess margins: in this case, a IIa lesion in the greater curvature of the antrum; B) the lesion margins are marked using the needle knife and coagulation current. Virtual chromoendoscopy is employed to facilitate mucosal pattern inspection and lesion delineation; C) the lesion is lifted away from the muscularis propria with submucosal injection; D) one or several access points to the submucosa are created around the lesion, using a needle-knife and blended current; E) et F) using the previously created access points, the IT-Knife is used to create a circumferential incision; G) the IT-knife is used to dissect the submucosal layer underneath the lesion; H) after complete resection, a coagulation forceps is used to coagulate the larger vessels in the mucosal defect.

## HISTOLOGICAL EVALUATION

The histopathological evaluation of the endoscopic resection specimen is the basis for the final decision between accepting endoscopic treatment as curative or proposing further surgery. To improve accurate assessment, specimens should ideally be pinned on cork or thick paper with pins to avoid shrinkage artifacts before being fixed in 4% formalin. The minimal requirements for the pathology report are:

- lesion size,
- histological type,
- grade: well-differentiated (G1), moderately differentiated (G2) and undifferentiated/diffuse type (G3)
- invasion depth: intraepithelial neoplasia (pTis), intramucosal adenocarcinoma (pTia) or submucosal adenocarcinoma (pT1b), and in the latter, submucosal invasion depth in μm should be measured (sm1 if ≤500 μm; sm2 if >500 μm)
- lymphovascular invasion,
- ulceration,
- vertical and horizontal resection margins.



Initial curative criteria for endoscopic resection were based on the limitations of EMR and included only differentiated adenocarcinomas of <20mm without ulceration or lymphovascular invasion. With the possibilities brought on by ESD, these criteria were found to be too strict, resulting in unnecessary surgery, as large surgical series of pT1 cancers found additional groups of lesions with very low risk of LNM. These were termed "expanded criteria" for endoscopic cure (providing en bloc and R0 resection):

- differentiated non-ulcerated intramucosal adenocarcinoma without lymphovascular invasion, of any size (LNM risk <0.5%);
- differentiated ulcerated intramucosal adenocarcinoma without lymphovascular invasion, ≤30 mm (LNM risk <0.5%);
- differentiated non-ulcerated superficial submucosal adenocarcinoma (≤500 μm invasion depth) without lymphovascular invasion, ≤30 mm (LNM risk <3%);
- undifferentiated non-ulcerated intramucosal adenocarcinoma without lymphovascular invasion, ≤20 mm (LNM risk <1%).

A particular situation is the case of a piecemeal resection or positive horizontal margin, as these cases do not increase the risk of LNM but have a high risk of local recurrence [32], which can in the majority of cases be re-treated with ESD.

Any patient who does not meet these criteria should be informed of the 2.5-20% risk of lymph node disease and gastrectomy with lymphadenectomy should be proposed, unless advanced age or significant comorbidities are a concern, in which case surgical morbi-mortality must be weighed against the risk of recurrence. In this regard, a scoring system based on non-curative resections submitted to surgery (eCura

system) was proposed, dividing patients into low-, medium- and high-risk groups for LNM based on lymphatic invasion, tumor size, deep submucosal invasion, venous invasion and positive vertical margins [33]. The system was validated and these subgroups are associated with differences in 5-year disease-specific survival (99.6, 96 and 91%, respectively). More importantly, in the low-risk group, 5-year disease-specific survival was very similar whether patients were operated or surveilled (99.7 vs 99.6%) [34], suggesting that in fragile patients, surveillance may be an option as long as the patient is informed of the risks and poor prognosis in the event of disease recurrence.

## FOLLOW-UP AFTER ENDOSCOPIC RESECTION

After a curative resection, the main concern during follow-up is the risk of metachronous lesions (10-20%); this is higher in older patients, those with multiple lesions and those with extensive pre-neoplastic conditions [27,35]. *Helicobacter pylori* should be eradicated when present as its eradication can reduce the incidence of new lesions (36). Since there are currently no other strategies proven to decrease the risk of metachronous lesions, management of these patients relies on regular endoscopic follow-up, as >85% of new lesions are amenable to endoscopic resection.



Most centers schedule a first endoscopy 3-6 months after ESD (to confirm scar healing and absence of residual/synchronous lesions) and annually thereafter, as there is evidence that longer intervals are associated with larger, more advanced lesions and higher rates of gastrectomy [37]. Given the low risk of LNM, in expanded criteria resections, staging baseline and follow-up CTs should also be considered.

In the case of local-risk resection (positive horizontal margins or piecemeal resection), scar biopsies and more frequent endoscopies in the first two years should be considered.

## CONCLUSION

Due to the widespread use of endoscopy and advanced imaging techniques, gastric cancer is increasingly being diagnosed at early stages associated with low LNM risk and potentially amenable to curative endoscopic resection.

Careful endoscopic evaluation by an experienced endoscopist is the main staging procedure before treatment, with other imaging techniques (CT or EUS) having a controversial role. ESD is the first-line technique for endoscopic resection of early gastric cancer, as it has a high rate of en bloc, R0, curative resections, with an acceptable safety profile and a positive impact on the quality of life compared to surgery.

Accurate histopathological assessment of the resection specimen is paramount for adequate post-resection management, since in lesions with high-risk criteria for LNM surgical lymphadenectomy must be considered. After a curative endoscopic resection, there is a considerable risk of developing metachronous lesions and endoscopic follow-up is necessary for early detection.

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# Organization of expert centers

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An expert center is defined as a working group of different specialists who have an experience in the field of gastric cancer and gastric carcinogenesis, capable of providing multidisciplinary care coordination with the aim of assuring an optimal outcome for patients with an increased risk of gastric cancer 1. This working group mainly includes gastroenterologists/endoscopists, experts in the detection and resection of gastric lesions, pathologists and biologists. This team has to take care of patients presenting low or high risk of gastric cancer or already presenting preneoplastic lesions. However, the strategy is to coordinate the different specialities and create a cohort of patients, which is the first step for creating a research network. This group of experts standardizes the process of care and develops the methods of teaching. According to the according to the European Cancer Organization (ECCO) 2, the essential requirements for the organization of an expert care center encompass multidisciplinary teamwork, patient care pathways, professional education and enrolment in clinical trials.

## MULTIDISCIPLINARY TEAM

A multidisciplinary team (MDT) should encompass different specialists in one center, including a gastroenterologist/endoscopist, bacteriologist, geneticist, surgeon and pathologist, who have experience in chronic gastritis and gastric preneoplastic lesions. This team will take care of the patients and discuss each case at regular meetings, use the most recent technologies and adequate treatment based on recent published guidelines. According to the ECCO recommendations, MDT members should see at least 200 cases with oeso-gastric cancer lesions annually 2.

Several studies have demonstrated the effectiveness of MDTs in improving efficiency of care delay and clinical outcome 3-5, as well as in reducing the number of unnecessary tests 6. The MDT organization prioritizes the resources in order to decrease the delay of treatment initiation. Clinical prioritization for referrals is a form of time scheduling. Prioritization can improve both the effectiveness and the equity in accessing health care. This approach has to be developed in close interac-

tion between primary care physicians and different specialists. It has been reported that almost one third of gastroscopies are inappropriate referrals [7-10]. In a recent retrospective study [8], as much as 43% of almost 86,000 repeated gastroscopies were inappropriately prescribed. A recent review showed that the prevalence of relevant findings was significantly higher in case of "appropriate" than "inappropriate" gastroscopies [9]. Likewise, data by Meggio *et al.* [10] seems to demonstrate that appropriateness was the main variable predicting the risk of relevant endoscopic finding (OR 9.29, $p<0.0001$), secondary to priority agreement between the primary care physicians and the specialists (OR 1.911, $p=0.03$). Another issue implicated in the use of this model was to guarantee timely high-priority referrals without affecting the normal supply of services.

Interventional endoscopy is also a part of the management of patients with early neoplastic gastric tumors. The gastroenterologist/endoscopist must be trained and accredited in diagnostic upper GI endoscopy [2]. Chromoendoscopy and high-definition video endoscopy must be used for diagnosis and treatment. The endoscopic resection techniques have to be mastered and the endoscopy unit must be subjected to appropriate regular audit. Among quality criteria, resection margin or right correct histological analysis highlight the close interaction between the endoscopist and the pathologist.



Pathology, especially using techniques of molecular pathology, plays a critical role in the diagnosis of gastric preneoplastic and neoplastic lesions [11]. Pathologists must have an expertise in the evaluation of gastric biopsies as well as EMR (endoscopic mucosal resection) /ESD (endoscopic submucosal dissection) specimens. Over the years, there has been a disagreement between the Western and the Japanese pathologists regarding the diagnosis of superficial gastric lesions, with a lack of inter-observer agreement in the differential diagnosis between reactive and dysplastic changes, between undefined or high-grade dysplasia and intramucosal carcinoma [12]. The pathologist reports have to detail the analysis of the resected tumor or the biopsies and must contain a list of items as recommended by professional organizations and internationally recognized classification used for histopathological diagnosis [13]. In case of indefinite OK dysplasia or suspicion of cancer, a second analysis must be performed internally or externally by national experts.

The development of professional relationships with ancillary services increases the use of evidence-based assessment. Improved standardization and less variability were seen after implementation of the MDT [6]. The responsibility for coordination of studies and diagnostic tests was consolidated within a single service with the greatest capacity.

## ORGANIZATION OF THE PATIENT CARE PATHWAY

In Western countries, screening programs targeting only the high-risk population (*figure 1*) seem to be more cost-effective than general screening programs, irrespec-

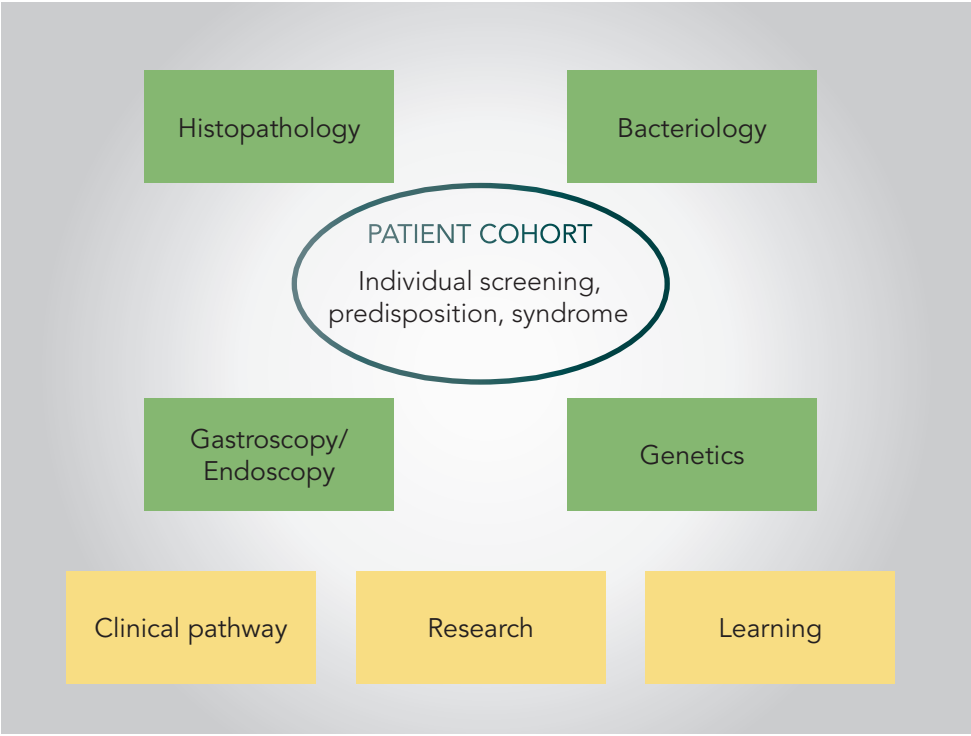


FIGURE 1. Patient care pathway in expert center.

tive of age or risk factors [14]. A risk-based approach to endoscopic screening of the upper gastro-intestinal tract (GIT) may be more cost-effective than general screening of asymptomatic low-risk individuals. Indeed, it is important to distinguish the general population from the patients with inherited cancer predisposition syndromes or first-degree relatives of gastric cancer patients, who also have to be managed by experts in genetic testing and counselling, working together with gastroenterologists. For this reason, it is important to stratify the risk of gastric cancer depending on the clinical criteria (sex, personal and family history, ethnic background, *H. pylori* infection, …) as well as on endoscopic and histological findings (atrophy, intestinal metaplasia, ...) in order to establish specific patient care pathways. Identification of the subjects at a very high risk of upper GIT cancer and the appropriate surveillance of these patients is the main objective. Once a patient is identified with preneoplastic lesions or cancer predisposition, an appropriate surveillance has to be initiated in order to prevent the development of cancer. For genetic predisposition syndromes, guidelines have been established recommending upper endoscopy as part of management [15, 16]. Patients with cancer predisposition have an increased risk for various tumor types, many of which could be detected early or even prevented through specialized screening and surveillance. Identification of individuals with genetic predisposition to cancer affects treatment of both the patients with cancer and their relatives. Geneticists are expected to use family history and tumor molecular data to perform genetic assessments for every patient with preneoplastic lesions (dysplasia, polyps) and be familiar with the diagnosis and management of individuals with hereditary cancer syndromes [17]. Individuals who carry associated mutations should benefit from consultation with multidisciplinary care teams composed of oncologist, geneticist, surgeon and gastroenterologist advisers. Furthermore, the expert center may collaborate with certified patient associations who represent users, particularly with genetic diseases. The involvement of patients in therapeutic programs is another way of favoring a care approach. This improves the care of patients and their families by developing community-hospital networks and collaboration between physicians and patient associations.



An expert center has to fulfill some quality criteria. Firstly, the center has to be well identified and easily available to the patients and to the professionals. Secondly, for a proper and detailed endoscopic assessment of the upper GIT, some performance measures need to be considered as described by the European Society of GI Endoscopy (ESGE), including key performance measures and minor performance measures (*table 1*). Certain standards, such as accurate photo-documentation, accurate terminology and nomenclature, as well as correct documentation, seem to be paramount for achieving a high-quality upper GIT endoscopic examination [18]. In the meta-analysis by Menon *et al.* [19], they have demonstrated a pooled missed rate of upper GIT cancer of 11.3%. Even in Japan, Shimodate *et al.* [20] showed that

75% of the newly diagnosed gastric cancers were evident in retrospectively analyzed images of prior gastroscopies of the same patients. Thirdly, time to treatment is also an important criterion of care quality, which is modified by various factors like institutional resources and regional practice patterns. Treatment strategies are decided on after a consensus among the MDT members during regular meetings. All MDT decisions must be documented and recorded in the patient's data. The core and extended MDTs must meet regularly to review the activity of the previous period based on the audited metrics, discuss changes in protocols and procedures and improve the performance of the unit/center. The MDT performance must be quality assured both internally and by external review with demonstration of cost-effectiveness of quality improvements. The essential requirements of the ECCO for a quality cancer care group strongly recommend participation in national or international accreditation programs [21].

TABLE 1. Major and minor criteria of quality of health care.

| Key performance measures | Minor performance measures |
|---|---|
| Instructions prior to UGI endoscopy | Minimum 7 min procedure time for first diagnostic UGI endoscopy and follow-up of preneoplastic lesions |
| Documentation of procedure duration | Minimum 1 min inspection time per cm |
| Accurate photodocumentation | Use of chromoendoscopy |
| Application of recommendations | Endoscopic resection |
| Accurate registration of complications after therapeutic UGI endoscopy | Prospective registration |

UGI endoscopy: Upper Gastrointestinal endoscopy.



## EDUCATION

An expert center should also play a central role in education. In endoscopy, the current trend in teaching before practical application on the patient is knowledge-based training, simulation followed by practical courses. These different types of training can involve mechanical models, live animal models, ex vivo (hybrid involving plastic and animal organs), practical training like e-learning and, more recently, computerized virtual reality simulators. These different models offer the possibility of acquiring technical or non-technical skills [22]. A Cochrane study concluded that these different types of training improve the skills, particularly of fellows [23].

Learning platforms, especially e-learning, have the advantage of allowing several gastroenterologists to be trained simultaneously in different parts of the world and

could therefore become an important tool for training, quality improvement and future developments in the field of endoscopy. In Japan, this endoscopic learning has already been shown to improve the detection of superficial gastric cancers [24-26]. The Portuguese teams have demonstrated the contribution of e-learning in the teaching and validation of endoscopic classification systems [27, 28]. Some studies have shown that web-based training significantly improves knowledge in chromoendoscopic characterization of the preneoplastic lesions in fellows as well as in MD groups. Significant average improvement rates of 21% [24] and 12% [25] have been demonstrated in the histological prediction of the main gastric lesions by white light and NBI with magnification through e-learning [24, 25]. The role of expert centers is to promulgate and spread the different ways of teaching to the medical community.

## RESEARCH CENTER

An expert center should be involved in clinical research programs, either through their own research or in programs supported by other centers included in research networks. The MDT meeting is an opportunity to assess all new patients for their eligibility to be included in academic or industry sponsored clinical trials. Collaboration between high volume centers and community hospitals is needed to identify the patients who could be included in clinical trials. Innovative study designs can be developed more efficiently by elaborating new diagnostic or therapeutic targets in the future [2]. Correlative biomarker research is a crucial part of all phases of clinical studies and requires close cooperation among the different physicians and pathologists/biologists and biobanks within research networks. The link between basic and clinical research is fundamental in order to develop new technologies or treatments, and this mission should also be supported by expert centers.

In conclusion, an expert center in the management of gastric precancerous lesions is based on a multidisciplinary team with high expertise in the field, and should combine the missions of optimal patient care using the best methods of diagnosis and treatment and dedicated patient pathways, education and research.



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| Abbreviation | Meaning |
|---|---|
| AFI | Autofluorescence Imaging |
| AG | Atrophic gastritis |
| AIG | Autoimmune gastritis |
| Anti-IFA | Anti-Intrisic Factor Antibodies |
| APCA | Antibodies against gastric parietal cells |
| ASR | Age-Standardized Rate |
| AST | Antimicrobial Susceptibility Testing |
| EGGIM | Endoscopic grading of gastric intestinal metaplasia |
| EMR | Endoscopic Mucosal Resection |
| ESD | Endoscopic Submucosal Dissection |
| EUS | Endoscopic ultrasonography |
| FIT test | Fecal Immunochemichal Test |
| GC | Gastric Cancer |
| GPL | Gastric precancerous lesions |
| GIM | Gastric Intestinal Metaplasia |
| GIT | Gastro-Intestinal tract |
| H&E | Hematoxylin and Eosin |
| HPSA test | *Helicobacter pylori* stool antigen test |
| IEE | Image-enhanced endoscopy |
| IM | Intestinal Metaplasia |
| IF | Intrisic factor |
| LBC | Light blue crest |

| Abbreviation | Meaning |
|---|---|
| LNM | Lymph node Metastatis |
| MAPS | MAnagement of epithelial Precancerous conditions and lesions in the Stomach |
| NBI | Narrow band imaging |
| NCGC | Non-cardia Gastric Cancer |
| OLGA | Operative Link on Gastritis Assessmenton |
| OLGIM | Operative Link on Gastritis Assessment based on Intestinal Metaplasia |
| pCLE | Probe-based confocal laser endomicroscopy |
| PGI | Pepsinogen I |
| PGII | Pepsinogen II |
| PPI | Proton pump inhibitors |
| SPGI | Serum levels of pepsinogens |
| TMI | Trimodal Imaging |
| TFF | Trefoil factor |
| WLE | White Light Endoscopy |

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