



CLINICAL PRACTICE GUIDELINES

Gastric cancer screening in low incidence populations: Position statement of AEG, SEED and SEAP[☆]



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Abstract This positioning document, sponsored by the Asociación Española de Gastroenterología (Spanish Association of Gastroenterology), the Sociedad Española de Endoscopia

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cancer

Digestiva (Spanish Society of Digestive Endoscopy) and the Sociedad Española de Anatomía Patológica (Spanish Society of Pathology), aims to establish recommendations for the screening of gastric cancer (GC) in low incidence populations, such as the Spanish. To establish the quality of the evidence and the levels of recommendation, we used the methodology based on the GRADE system (Grading of Recommendations Assessment, Development and Evaluation). We obtained a consensus among experts using a Delphi method. The document evaluates screening in the general population, individuals with relatives with GC and subjects with GC precursor lesions (GCPL). The goal of the interventions should be to reduce GC-related mortality. We recommend the use of the OLGIM classification and to determine the intestinal metaplasia (IM) subtype in the evaluation of GCPL. We do not recommend establishing endoscopic mass screening for GC or *H. pylori*. However, the document strongly recommends treating *H. pylori* if the infection is detected, and investigation and treatment in individuals with a family history of GC or with GCPL. Meanwhile, we recommend against the use of serological tests to detect GCPL. Endoscopic screening is suggested only in individuals that meet familial GC criteria. As for individuals with GCPL, endoscopic surveillance is only suggested in extensive IM associated with additional risk factors (incomplete IM and/or a family history of GC), after resection of dysplastic lesions or in patients with dysplasia without visible lesion after a high-quality gastroscopy with chromoendoscopy.

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PALABRAS CLAVE

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Documento de posicionamiento de la AEG, la SEED y la SEAP sobre cribado de cáncer gástrico en poblaciones con baja incidencia

Resumen Este documento de posicionamiento, auspiciado por la Asociación Española de Gastroenterología, la Sociedad Española de Endoscopia Digestiva y la Sociedad Española de Anatomía Patológica tiene como objetivo establecer recomendaciones para el cribado del cáncer gástrico (CG) en poblaciones con incidencia baja, como la española. Para establecer la calidad de la evidencia y los niveles de recomendación se ha utilizado la metodología basada en el sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*). Se obtuvo el consenso entre expertos mediante un método Delphi. El documento evalúa el cribado en población general, individuos con familiares con CG y lesiones precursoras de CG (LPCG). El objetivo de las intervenciones debe ser la reducción de la mortalidad por CG. Se recomienda el uso de la clasificación OLGIM y determinar el subtipo de metaplasia intestinal (MI) para evaluar las LPCG. No se recomienda establecer cribado poblacional endoscópico de CG ni de *H. pylori*. Sin embargo, el documento establece una recomendación fuerte para el tratamiento de *H. pylori* si se detecta la infección, y su investigación y tratamiento en individuos con antecedentes familiares de CG o con LPCG. En cambio, no se recomienda el uso de tests serológicos para detectar LPCG. Se sugiere cribado endoscópico únicamente en los individuos con criterios de CG familiar. En cuanto a los individuos con LPCG sólo se sugiere vigilancia endoscópica ante MI extensa asociada a algún factor de riesgo adicional (MI incompleta y/o antecedentes familiares de CG), tras la resección de lesiones displásicas o en pacientes con displasia sin lesión visible tras una endoscopia digestiva alta de calidad con cromosendoscopia.

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Introduction

Gastric cancer (GC) is the second most common type of gastrointestinal cancer. In Spain, as in the rest of Europe, the incidence of GC is at levels accepted as low. In 2018, there were an estimated 7765 new cases of GC, with an incidence rate adjusted to the world population of 9.2 cases/100,000 people in males and 4.3/100,000 people in females, and the adjusted mortality rates were 6.1/100,000 and 2.8/100,000,

respectively.¹ The incidence has been gradually decreasing in recent decades.

GC has a poor prognosis and remains associated with a high mortality rate,² with five-year age-adjusted survival around 21% in males and 26% in females.³ This high mortality rate is due to multiple factors, including the fact that diagnosis is made in advanced stages and a limited response to chemotherapy. In an attempt to reduce the impact of GC, strategies for screening and treating the main cause of

GC, *Helicobacter pylori*, have been put forward.^{3–8} Additionally, early detection programmes have been implemented in populations with a high prevalence of GC and surveillance programmes have been proposed in patients with precancerous lesions or conditions associated with an increased risk of developing GC.⁹

Gastric carcinogenesis is associated with *H. pylori* and occurs through a sequence of GC precursor lesions (GCPLs): atrophic gastritis, intestinal metaplasia (IM) and dysplasia.⁹ Patients with these lesions could be candidates for measures to reduce the risk of GC, such as eradication of *H. pylori*, surveillance with upper gastrointestinal endoscopy (UGIE) and resection of lesions with a high risk of malignancy.¹⁰ The aim of any of these measures should be to reduce GC mortality rates in this group of high-risk patients through early detection and/or reduction in the incidence.

In recent years, many position statements have been published with varying points of view on important aspects of screening. The aim of this position statement is to put forward a set of consensus clinical practice recommendations after assessing the evidence and the different published clinical practice guidelines. The document deals with two different aspects in particular:

Determining which factors lead to an increased risk of GC, in particular family history of GC and histological precursor lesions of GC. In this regard, the histological criteria for the diagnosis of GC are assessed.

Assessing the efficacy of implementing the different strategies for reducing the incidence and/or mortality rate of GC in these situations (eradication of *H. pylori* and endoscopic surveillance) versus not implementing them, and making recommendations on their relevance.

These recommendations are aimed at preventing GC in low-incidence populations, which reflects the epidemiological situation in Spain. The following lie outside the scope of this document: prevention of diffuse GC, cardia GC and gastric neuroendocrine tumours; diagnosis of GC; diagnosis and surveillance in hereditary syndromes with predisposition to GC; and treatment of precursor lesions. This position statement is the fruit of a collaboration between the Asociación Española de Gastroenterología [Spanish Association of Gastroenterology] (AEG), the Sociedad Española de Endoscopia Digestiva [Spanish Association of Gastrointestinal Endoscopy] (SEED) and the Sociedad Española de Anatomía Patológica [Spanish Association of Pathology] (SEAP) to arrive at a set of unified criteria and recommendations for clinical gastroenterologists, endoscopists and pathologists.

Methods

A working group of methodologists and experts from these associations was set up to research and review the evidence. The working group put forward the clinically important questions that are addressed in the statement. The GC incidence and mortality were determined to be important objectives.

To establish the levels of evidence and the strength of recommendations for the different questions addressed, we used the methodology based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group system.¹¹ In so doing, we considered not only evidence quality, but also the risk-benefit balance, costs,

and people's values and preferences. No recommendations were formulated or graded in the sections where this was not necessary, i.e. definitions and assessment of the GCPLs.

Once the recommendations were made, the agreement among the members of the working group was assessed. A consensus was achieved using the Delphi method. The recommendations were evaluated by the panel members using a Likert scale (1: strongly disagree; 2: disagree; 3: undecided; 4: agree; and 5: strongly agree). In the event of a disagreement, the recommendations were reformulated and voted on again. Those obtaining a final average agreement ≥ 4 (agree or strongly agree) were presented and substantiated. The first round of the Delphi consensus was done in November 2019 using the REDCap electronic data capture tools hosted at the AEG (www.aegastro.es).¹² After reformulating the recommendations with agreement < 4 , a second round was held over two videoconferences on 22 May and 1 June 2020. Table 1 shows the final recommendations, together with an evaluation of the evidence, the strength of the recommendation and the degree of agreement. An algorithm is also included (Fig. 1). This position statement was approved by the boards of directors of the three scientific associations involved.

Definitions

At-risk population for GC. The at-risk population for GC is considered to be people with GCPLs who are potentially at increased risk of developing cancer.

Gastric atrophy. This is defined as loss of "appropriate glands" in the gastric mucosa.¹³ and includes two phenotypes: a) non-metaplastic atrophy, where there is a reduced number of glands in the gastric mucosa but no changes in the original type of glandular epithelium; and b) metaplastic atrophy, in which the normal glands in each gastric region are replaced by another gland type not typical of that region, including pseudopyloric metaplasia on mucosa in the corpus or fundus and intestinal metaplasia (IM).¹³

Intestinal metaplasia (IM). This is defined as replacement of the glandular and foveolar epithelium of the gastric mucosa by intestinal epithelium.¹⁴ The most widely used classification is the one that distinguishes between two types of IM: a) *complete* IM, in which the gastric mucosa acquires the phenotype typical of the small bowel mucosa; and b) *incomplete* IM, in which the gastric mucosa appears similar to the colonic mucosa.

Indefinite for dysplasia/neoplasia / dysplasia / intraepithelial neoplasia / non-invasive neoplasia. Dysplasia is an epithelial proliferation with definite cytological and architectural atypia, but no evidence of infiltration.^{15–17} Depending on the degree of abnormality in the architecture and the cytological atypia, dysplastic lesions are classified as low-grade dysplasia, high-grade dysplasia or carcinoma *in situ*. The diagnosis "indefinite for neoplasia/dysplasia" is used in the presence of an inflammatory component or artefacts precluding a diagnosis of dysplasia, which should not be considered innocuous, as 26.8% of resected lesions were found to be cancerous (5% adenomas and 21.8% carcinomas).¹⁸

Familial GC with no known genetic cause. One of the clinical situations involving higher risk is familial GC (FGC),

Table 1 Recommendations of the position statement on gastric cancer screening in low-incidence populations. Includes grade of evidence, strength of recommendation and final expert agreement.

Recommendation	Grade of evidence	Strength of recommendation	Agreement (1–5)
<i>General matters and histological diagnosis</i>			
1. The aim of interventions in patients with GCPLs must be to reduce GC mortality			5
2.a. It is suggested that screening programmes in patients over 75 be discontinued or not started	Very low	Weak in favour	4.75
2.b. Discontinuing or not starting screening programmes is suggested in patients whose comorbidity entails an estimated life expectancy of less than 10 years	Very low	Weak in favour	5
3. Using the OLGIM staging system and determining the IM subtype in GCPL pathology reports are recommended			5
4. Proper staging of GCPLs can be done regardless of <i>H. pylori</i> eradication status			4.64
5. It is not necessary to discontinue PPIs for proper staging of GCPLs. However, it is recommended that PPIs be discontinued for proper detection of <i>H. pylori</i>	Low	Strong in favour	5
6. It is recommended that dysplasia always be confirmed by a second pathologist			5
<i>Prevention in general population</i>			
7. Population-based strategies should not be implemented to detect and subsequently eradicate <i>H.pylori</i> infection	Low	Weak against	5
8. In patients with <i>H.pylori</i> infection, treatment is recommended, regardless of the reason for diagnosis	High	Strong in favour	4.64
9. Patients on long-term treatment with PPIs should be tested for <i>H.pylori</i> , with the aim of eradicating it before starting PPI treatment	Low	Weak in favour	5
10. The use of serological tests for detection of GCPLs in the general population is not recommended	Low	Strong against	5
11. Population-based endoscopic screening for GC should not be implemented in Spain	Very low	Strong against	5
<i>Prevention in individuals with GC clustering</i>			
12. Testing for and treatment of <i>H.pylori</i> infection is recommended in individuals with an FDR with GC	High	Strong in favour	5
13. Routine endoscopic screening is not recommended in patients with a history of but no criteria for familial GC	Low	Strong against	4.75
14. In individuals with familial clustering of GC, hereditary syndromes associated with GC should be ruled out	Very low	Strong in favour	5
15. In those who meet the criteria for familial GC, endoscopic GC screening is recommended	Very low	Weak in favour	4.25
<i>Prevention in patients with GCPLs</i>			
16. It is recommended that patients with gastric atrophy or IM be tested and treated for <i>H.pylori</i> infection	Moderate	Strong in favour	4.64
17. It is recommended that patients be tested and treated for <i>H.pylori</i> infection following endoscopic resection of dysplasia or carcinoma in situ	High	Strong in favour	4.64
18. Endoscopic surveillance is not recommended in patients with gastric atrophy without IM, regardless of extent	Very low	Strong against	4.8
19. A high-quality UGIE and staging by OLGIM at 6–12 months are recommended when IM is diagnosed in a low-quality UGIE	Low	Strong in favour	4.8
20.a. Endoscopic surveillance is not recommended in patients with OLGIM I-II (focal IM)	Low	Strong against	4.75
20.b. Not performing endoscopic surveillance is suggested in patients with OLGIM III-IV (extensive IM) without additional risk factors	Very low	Weak against	4.08
20.c. Endoscopic surveillance every three years is suggested in patients with extensive IM (OLGIM III-IV) associated with incomplete IM or a family history of GC	Very low	Weak in favour	4.64

Table 1 (Continued)

Recommendation	Grade of evidence	Strength of recommendation	Agreement (1–5)
21. Resection of visible lesions with dysplasia is recommended for accurate histological diagnosis	High	Strong in favour	4.83
22. Quality endoscopy is recommended for reassessment within 6 months following a diagnosis of dysplasia of any grade	Very low	Strong in favour	4.66
23.a. It is suggested that endoscopic surveillance be done annually for 2 years and according to baseline risk thereafter following endoscopic resection of low-grade dysplasia	Very low	Weak in favour	4.41
23.b. Following resection of high-grade dysplasia or carcinoma in situ, it is suggested that endoscopic surveillance be done every six months for the first year, then annually for 3 years and according to baseline risk thereafter	Very low	Weak in favour	4.42
24. With a diagnosis of dysplasia without visible lesions after a quality UGIE with chromoendoscopy, it is suggested that endoscopic follow-up be done at 6 months (high-grade dysplasia) to 12 months (low-grade dysplasia)	Very low	Weak in favour	4.46

FDR: first-degree relative; GC: gastric cancer; GCPL: gastric cancer precursor lesion; IM: intestinal metaplasia; PPI: proton pump inhibitor.

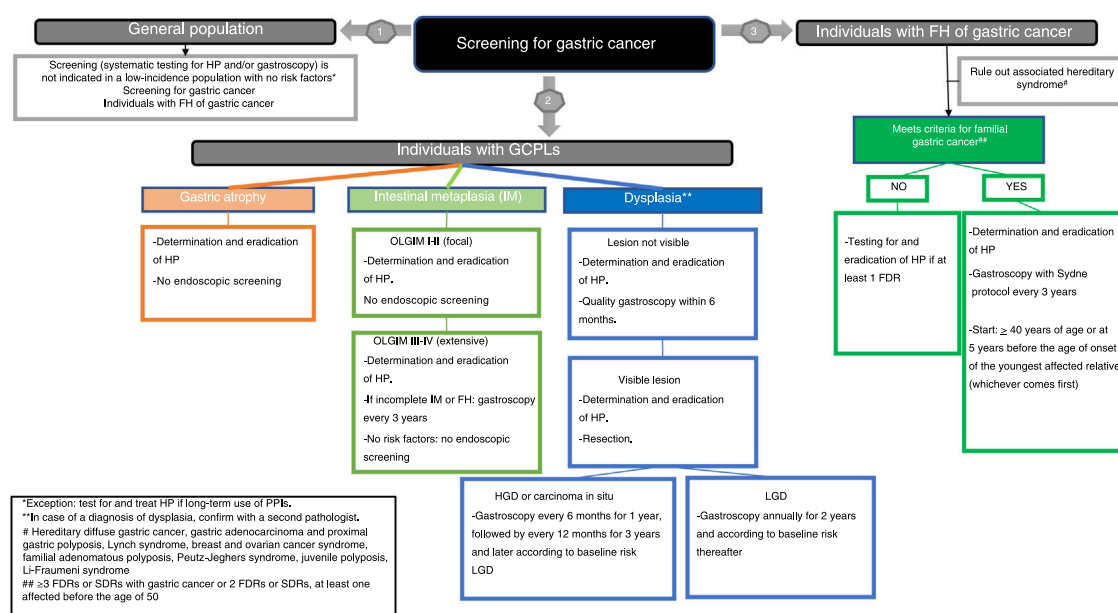


Figure 1 Gastric cancer screening strategy in a low-incidence population.

in which familial clustering of GC of intestinal histology is seen with no identified hereditary cause. It is defined by the following criteria: a) >3 first-degree relatives (FDRs) or second-degree relatives (SDRs) with GC, regardless of age, or b) >2 FDRs or SDRs with GC, at least one of whom is under 50.¹⁹

Intramucosal carcinoma/invasive intramucosal carcinoma. This is a carcinoma that invades the lamina propria or *muscularis mucosae*, without submucosal infiltration (pT1a).

Early gastric cancer (EGC). This includes pT1a and pT1b (with submucosal infiltration), and is independent of lymph node status. Usually, there are distinctive architectural abnormalities, such as marked glandular density, a cribriform pattern, budding, glandular proliferation or desmoplasia.

Quality UGIE. This refers to an endoscopic examination performed with a high-definition endoscope following a systematic protocol with representative photos of all regions and lesions, with a minimum duration of 7 min.^{20–22}

Population risk of GC. Risk is defined based on age-adjusted incidence rate. A region is defined as high risk when the annual incidence is greater than 20/100,000 inhabitants, intermediate risk if it is 10–20/100,000 and low risk if it is less than 10/100,000.²³

Results

The expert group selected and answered the following questions:

Table 2 Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) classification.

	Gastric corpus				
		No IM (score 0)	Mild IM (score 1)	Moderate IM (score 2)	Severe IM (score 3)
Antrum (including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage III
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

IM: intestinal metaplasia.
Adapted from Capelle et al.³⁰

General

1. What should be the objective of the interventions evaluated in patients with GCPLs?

The objective of the interventions in patients with GCPLs must be to reduce GC mortality.

Agreement 5.

2. Up to what age is gastric cancer screening recommended?

It is suggested that screening programmes in patients over 75 be discontinued or not started.

Very low quality of evidence, weak recommendation in favour.

Agreement 4.75.

Discontinuing or not starting screening programmes is suggested in patients whose comorbidity entails an estimated life expectancy of less than 10 years.

Very low quality of evidence, weak recommendation in favour.

Agreement 5.

Evidence

The World Health Organization (WHO) defines screening as presumptive identification of unrecognised diseases or defects by means of tests, examinations or other procedures that can be done quickly and easily in the target population. Screening is used to detect serious chronic diseases such as cancer, in which a reduction in mortality rates is the primary objective. The requirements to determine the suitability of a screening strategy were initially defined by WHO in 1968 and subsequently updated by the UK National Screening Committee in 2015.^{24,25} In the case of cancer, the objectives are to reduce the incidence and, primarily, cancer-specific mortality. The effect on mortality should be determined within clinical trials, population registries and registries specific to the population subject to screening. As this means monitoring a target population for many years, the results will not be seen in the short term, so, once the screening programme has started, it is recommended that intermediate indicators be monitored.²⁶ In the specific case of GC screening, early detection and treatment of gastric high-grade lesions and carcinomas in situ, in addition to interval cancer rates, could be an effective intermediate indicator.

The benefit of screening the general population may be limited by age and comorbidity, both of which reduce the life expectancy of the patient and increase the risks and complications of invasive procedures. Screening is unlikely to significantly modify life expectancy when this is less than 10 years due to a patient's underlying disease. As an example, the risk of death in Spain at the age of 75 is 2.1% per 100 individuals per year and increases rapidly; by the age of 80 it is already 3.7 per 100 per year.²⁷ Furthermore, the risk of procedures and potential surgery also increases with comorbidity and age. For all these reasons, it is suggested that GC screening be discontinued — or not started in the first place — at 75 years of age or when the patient's life expectancy is clearly less than ten years.²⁸

Histological diagnosis

3. Which histological method is recommended for classifying risk?

Using the Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) staging system and determining the IM subtype in GCPL pathology reports are recommended.

Agreement 5.

Evidence

The Sydney classification¹⁴ allows semi-quantitative assessment of the severity of precursor lesions. However, it does not provide prognostic information to help identify patients with a higher risk of lesion progression in clinical practice. For this reason, two systems have been proposed for histological grading and staging of chronic gastritis: OLGA (Operative Link for Gastritis Assessment),²⁹ based on the extent and severity of gastric atrophy and not distinguishing non-metaplastic from metaplastic atrophy; and OLGIM,³⁰ based exclusively on the extent and severity of the IM (Table 2). The two systems coincide in that the risk of cancer is concentrated in advanced stages (OLGA III/IV or OLGIM III/IV). Two cross-sectional studies^{31,32} and a cohort study³³ using the OLGA system and a follow-up study³⁴ using the OLGIM system have highlighted their ease of use and utility in identifying patients at risk of progression. Both systems are currently recommended.¹⁰ However, whereas the diagnosis of atrophy shows great intra- and inter-observer variability,^{35,36} the level of agreement for IM is almost perfect — three times higher than for atrophy.³⁰ Therefore, some authors believe that the OLGIM system is more appropriate than the OLGA system for identifying patients with GCPLs at high risk of progression. Thus, the extent of the IM is the most reliable diagnostic parameter for predicting the risk of GC.³⁰ Additionally, incomplete IM is a significant marker of progression of lesions and development of gastric carcinoma,^{37–39} and the follow-up of patients with incomplete IM may increase the likelihood of diagnosing early gastric cancer (EGC).^{40,41} After *H. pylori* eradication, patients with incomplete IM have a higher risk of developing GC than those with complete IM after 12 years of follow-up (odds ratio [OR]: 11.3; 95% confidence interval [CI]: 1.4–91.4).⁴² Moreover, the finding of incomplete IM in a gastric biopsy is an indicator of extensive IM.^{38,43} Therefore, IM type should be routinely included in pathology reports.

Expert opinion

Both the OLGA and OLGIM systems enable classification of risk in patients with GCPLs based on severity and extent of gastric atrophy and IM, respectively. The two systems coincide in that stage III and IV patients are at high risk of progression to GC. The low intra- and inter-observer diagnostic agreement in the case of atrophy compared to the almost perfect diagnostic agreement for IM make the OLGIM system the most reliable diagnostic parameter for predicting the risk of GC. Determining the presence of incomplete IM may provide additional information on GC risk.

4. Is it necessary to eradicate *H. pylori* to properly stage GCPLs?

*GCPLs can be properly staged regardless of *H. pylori* eradication status.*

Agreement 4.64.

A systematic review and two meta-analyses showed that eradication of *H. pylori* improved gastric histology and even normalised it in the early stages of the disease.⁴⁴⁻⁴⁶ In these stages, chronic gastritis and gastric atrophy without metaplasia were found to decrease in severity one to two years after *H. pylori* eradication,⁴⁵ although in the case of atrophy this could vary by extent and location.⁴⁶ The two meta-analyses concluded that there is no significant improvement in IM after *H. pylori* eradication.^{44,46} However, a more recent randomised clinical trial (RCT) showed that, in patients with GCPLs, eradication of *H. pylori* achieved regression of both atrophy and IM after both six and twelve years of follow-up in a significant percentage of patients.^{47,48} The same study also showed regression of low-grade dysplasia (LGD) in some cases.^{47,48} By contrast, regression of high-grade dysplasia (HGD) is very rare.⁴⁹ Considering that patients who may be candidates for monitoring are those with epithelial dysplasia, atrophy and/or extensive IM and these lesions do not vary in the short term, despite *H. pylori* eradication treatment, prior eradication would not be necessary to perform proper staging of these patients.

5. Is it necessary to discontinue proton pump inhibitors (PPIs) for proper staging of GCPLs?

It is not necessary to discontinue PPIs for proper staging of GCPLs. However, it is recommended that PPIs be discontinued for proper detection of H. pylori.

Low quality of evidence, strong recommendation in favour.

Agreement 5.

There are no studies specifically assessing the need to discontinue PPIs for quality gastroscopy. There are also no studies showing that PPIs interfere with the histological diagnosis of atrophy and/or IM.⁵⁰ In studies in rodents, using PPIs increased the risk of developing atrophic gastritis in the corpus and cancer,⁵¹ probably due to PPIs' acidity-inhibiting effect.⁵² There are no specific studies assessing whether or not PPI treatment affects accurate diagnosis of GCPLs, but multiple studies have shown that the use of PPIs can mask the presence of *H. pylori*.⁵³

Expert opinion

The quality of evidence for the available data is very low and does not support a recommendation on the need to discontinue PPIs prior to performing follow-up gastroscopy of GCPLs. It is necessary, however, to discontinue PPIs at least two weeks prior to the initial endoscopy so as to avoid false negative diagnoses of *H. pylori* as a result of these drugs.⁵⁴

6. When should dysplasia be confirmed by a second pathologist?

It is recommended that dysplasia always be confirmed by a second pathologist.

Agreement 5.

The Padova classification of gastric dysplasia shows good reproducibility and minimal inter-observer variability among pathologists with experience in gastrointestinal diseases.¹⁷ This classification made it possible to unify the terminology between Western and Japanese pathologists. The Vienna classification is currently the most widely used.¹⁶ In 2009, the WHO¹⁵ modified the classification of dysplasia, renaming it intraepithelial neoplasia, maintaining the three diagnostic

categories proposed in the Padova classification due to their ease of use: negative for intraepithelial neoplasia; indefinite for intraepithelial neoplasia; and high-grade/low-grade intraepithelial neoplasia.⁴⁹ Where the diagnosis is indefinite for dysplasia, a repeat biopsy is recommended. Although the prognosis of indefinite for dysplasia is usually benign, histological review by a second pathologist with experience in gastrointestinal pathology is recommended, as up to 26.8% of resected lesions with a diagnosis of indefinite for dysplasia/neoplasia were cancerous^{18,55,56} and review of the diagnosis of indefinite for dysplasia by expert pathologists changed the diagnosis to dysplasia in 11/46 patients, especially in those with risk factors.^{44,55,56} The diagnostic criteria for gastric intraepithelial neoplasia are a matter of global debate, with kappa values ranging from 0.74 to 1, depending on the institution. The overall kappa value is 0.83, indicating excellent agreement. However, the agreement for the different diagnoses is 91.5% for carcinoma, 86.3% for low-grade dysplasia and 50.8% for high-grade dysplasia. This shows that the diagnostic criteria for carcinoma are more reproducible than those for dysplasia; therefore, dysplasia should always be confirmed by a second pathologist.⁵⁷

Expert opinion

The reproducibility of the dysplasia classification is far less certain among non-expert pathologists. For this reason, a second opinion should be sought when the histological findings indicate the need for endoscopic treatment and in cases with a diagnosis of indefinite for dysplasia, dysplasia of any grade or carcinoma in non-targeted random biopsies.^{18,57}

GC screening in general population

7. Are *H. pylori* screening and treatment recommended in the general population to reduce gastric cancer mortality?

Population-based strategies should not be implemented to detect and subsequently eradicate H. pylori infection.

Low quality of evidence, weak recommendation against.

Agreement 5.

8. Is eradication therapy recommended in patients with *H. pylori* infection?

Treatment of H. pylori infection is recommended, regardless of the reason for diagnosis.

High quality of evidence, strong recommendation in favour.

Agreement 4.64.**Evidence**

Eradication of *H. pylori* in the general population in high-prevalence areas significantly reduces GC incidence and mortality.³⁻⁵ The results come from both meta-analysis of RCTs and meta-analysis of observational studies.^{3,6,58} The reduction in the risk of GC is very similar in all studies (OR: 0.46 for observational studies; 0.54 for RCTs) with a number needed to treat (NNT) of 72 to prevent a case of GC and 137 to prevent a GC-related death.⁶ Cost-effectiveness studies are highly heterogeneous but agree that eradication is cost-effective.⁵⁹ Nevertheless, there is no evidence on the effect of implementation of population-based strategies for *H. pylori* detection and subsequent eradication, especially in areas with a low incidence of GC such as Spain.⁶⁰

Expert opinion

The level of evidence on the effect of *H. pylori* eradication on reducing the incidence of GC is strong, with a NNT of approximately 125 to prevent a case of GC. Non-invasive, high-precision tests for the diagnosis of *H. pylori* and treatments with high eradication rates are available. Furthermore, eradication of *H. pylori* is recommended in Spain as a treatment strategy for uninvestigated dyspepsia, peptic ulcer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Therefore, eradicating *H. pylori* in a patient with known infection is justified at the individual level, regardless of the reason that led to the diagnosis.⁵⁴

There are, however, factors against recommending a population-based screening programme: a) The acceptability of diagnostic tests for and, in particular, treatment of *H. pylori* in asymptomatic individuals is unknown; b) The potential rates of the population participating in a screening programme are therefore unknown; and c) There are also no data on the effects on resource use, psychological impact or efficacy in a population with a low incidence of GC⁶⁰ like that of Spain. Therefore, the recommendation with regard to implementation of population-based strategies is weak against it, except within prospective studies, preferably clinical trials. The panel advises a viability assessment of the different population-based treatment options in Spain using models. For this type of model to be reliable, the actual prevalence of *H. pylori* at the present time needs to be determined, as the available data are not recent and the prevalence of infection is lower in younger cohorts.⁶¹

9. Is it necessary to test for *H. pylori* infection in patients on long-term treatment with PPIs?

Patients on long-term treatment with PPIs should be tested for H. pylori, with the aim of eradicating it before starting PPI treatment.

Low quality of evidence, weak recommendation in favour.

Agreement 5.

Evidence

Long-term use of PPIs worsens atrophic gastritis in the corpus in patients with *H. pylori*. This may increase the risk of GC, according to the results of a case-control study that included patients with reflux disease and *H. pylori* who underwent long-term treatment with PPIs versus fundoplication (81% versus 59%; $p = 0.007$).^{62,63} Moreover, in studies in rodents, using PPIs increased the risk of developing atrophic gastritis in the corpus and cancer,⁵¹ probably due to PPIs' acidity-inhibiting effect.⁵² According to a recent review of 16 studies in 1920 patients who received long-term treatment with PPIs, patients with *H. pylori* have a higher risk of atrophic gastritis in the corpus than those without.⁶⁴

Expert opinion

Although there is currently no clear evidence that PPIs increase the risk of GC, it is known that long-term use of PPIs in *H. pylori*-infected patients increases the risk of progression to GCPLs. Given the association between GCPLs and GC, as a precautionary measure, young patients requiring prolonged treatment with PPIs should be tested for *H. pylori* and treated if positive.⁷ *H. pylori* treatment has very low morbidity and mortality rates, and the associated finan-

cial costs are low, while the potential long-term benefit is high.⁵⁴ Nevertheless, it does not seem necessary to recommend *H. pylori* testing in the older population requiring ongoing treatment with PPIs, given the lack of evidence on the preventive effect in this population.

Use of serological tests for detection of GCPLs

10. Are serological tests recommended for detection of GCPLs?

The use of serological tests for detection of GCPLs in the general population is not recommended.

Low quality of evidence, strong recommendation against.

Agreement 5.

Evidence

Determination of circulating pepsinogen I/II has been suggested as a useful test for detecting patients with precancerous lesions. Two meta-analyses have reviewed the benefits of serological tests, finding a sensitivity of 60%-69% and a specificity of 88%-89% for the diagnosis of precancerous lesions.^{65,66} Other combinations have been suggested which include clinical data plus a combination of serology for *H. pylori*, pepsinogen and gastrin. The sensitivity and specificity of this classification are similar to those with the use of pepsinogen alone.⁶⁷ Studies in Spain using a diagnostic test combining pepsinogen, gastrin-17 and serology for *H. pylori* have shown even lower diagnostic precision, with a sensitivity of 50% and a specificity of 80%.⁶⁷ Knowing the prevalence of GCPLs is important when assessing the efficacy of a potential screening programme. Although the quality of the data is very heterogeneous, the prevalence in routine endoscopies of advanced lesions with a significant risk of progression to GC — including extensive IM and dysplasia — can be estimated at 7%.⁶⁸ In Spain, the prevalence of advanced lesions was even lower — 4% in a series by McNicholl et al.⁶⁹ Evaluation of serological tests is complicated by the varied methodology used in different studies.

Expert opinion

The population-based use of serological tests with low sensitivity and specificity <90% for detection of GCPLs in the context of a low prevalence (below 10%) would, on the one hand, generate a very high number of individuals with false positive results who will require endoscopy and, on the other hand, mean that only half of GCPLs would be detected.⁶⁹ To this it must be added that there is no evidence that screening for advanced lesions prevents GC. Therefore, if the efficacy of GCPL screening in preventing GC has not been demonstrated, the case for serological screening of the general population to detect GCPLs should be rejected.

Endoscopic screening

11. Is endoscopic screening in the general population recommended for preventing GC?

Population-based endoscopic screening for GC should not be implemented in Spain.

Very low quality of evidence, strong recommendation against.

Agreement 5.**Evidence**

Three-quarters of all new cases of and deaths due to GC occur in Asian countries, particularly China, Japan and Korea. In 1960, Japan began a massive annual radiological screening programme for GC. Since then, screening has been introduced in other countries by way of periodic UGIE. The evidence on the efficacy of such screening is moderate, and the results are not homogeneous. In Japan, several case-control and cohort studies, primarily conducted between 1980 and 2000, showed a 40%–60% reduction in GC mortality with radiological screening.⁷⁰ However, subsequent studies have not confirmed an association between radiological study and a reduction in mortality.⁷⁰

Clinical and epidemiological studies have shown that the accuracy of upper endoscopy is better than that of radiology.⁷⁰ However, there is no definitive evidence to show that endoscopic GC screening reduces mortality rates. In China, a prospective study on endoscopic surveillance in high-risk populations showed no reduction in GC mortality (standard mortality ratio 1.01; 95% CI: 0.77–1.57).⁷¹ By contrast, Hamashima et al.⁷² found a 30% reduction in GC mortality in the population subjected to endoscopic screening in Japan. Jun et al.⁷³ analysed the effect of the Korean national screening programme in a case-control study. Twice-yearly endoscopy significantly reduced GC mortality by approximately 50% (OR: 0.53; 95% CI: 0.51–0.56), whereas the barium study had no effect (OR: 0.98; 95% CI: 0.95–1.01). The data from this study therefore suggest that screening in high-risk populations does have an effect on mortality. However, this type of study is subject to a considerable risk of bias. In summary, the evidence in favour of screening in high-risk populations is limited. There are no data on the efficacy of population-based screening in low-risk areas.

Cost-effectiveness studies have focused on endoscopic IM screening and follow-up of high-risk patients with extensive metaplasia. These studies have shown that cost-effectiveness depends on the prevalence of extensive IM and the rate of progression from metaplasia to cancer, and have suggested that screening could be cost-effective in medium- and high-risk populations. Different strategies for detecting IM by endoscopy have been assessed using cost-effectiveness models. Most have suggested that it is not a cost-effective strategy in low-risk populations. Two cost-effectiveness studies have suggested that screening for GC and IM by upper endoscopy at the time of colonoscopy for colon cancer screening, with subsequent surveillance of GCPLs, could be cost-effective in medium- and high-risk areas.^{10,74} A study by Pimentel-Nunes study suggested that screening could be effective in risk groups with an annual incidence of GC of more than 10 cases per 100,000 people per year. According to these data and the prevalence published in Spain, endoscopic screening could be useful only in selected high-risk populations in certain areas of Castile-Leon and Galicia.^{75,76}

Expert opinion

There are factors against recommending the implementation of a population-based screening programme with

endoscopy. The potential rates of participation of the population in a screening programme are unknown. There are also no data on the effects on resource use, psychological impact or efficacy in a population with a low incidence of GC like that of Spain. The available data are based on indirect cost-effectiveness studies. They are heterogeneous and suggest that endoscopic screening for GC and IM is not effective in low-risk populations. There are neither clinical data to support screening nor solid data on which to base the assumptions of cost-effectiveness studies.

Patients with a family history of GC

12. Should patients with an FDR with GC be tested and treated for *H. pylori*?

Testing for and treatment of H. pylori infection is recommended in individuals with an FDR with GC.

High quality of evidence, strong recommendation in favour.

Agreement 5.

13. Is endoscopic screening recommended in patients with a family history of GC but no criteria for familial GC?

Routine endoscopic screening is not recommended in patients with a history of but no criteria for familial GC.

Low quality of evidence, strong recommendation against.

Agreement 4.75.

14. Is a family study necessary in patients with criteria for familial GC?

In individuals with familial clustering of GC, hereditary syndromes associated with GC should be ruled out.

Very low quality of evidence, strong recommendation in favour.

Agreement 5.

15. Is endoscopic screening recommended in familial GC with no known genetic cause?

In those who meet the criteria for familial GC, endoscopic GC screening is recommended.

Very low quality of evidence, weak recommendation in favour.

Agreement 4.25.

Evidence

The aetiology of GC is multifactorial; the main environmental agents include *H. pylori*, diet and smoking. Although most cases of GC are sporadic, familial clustering is found in approximately 10% of cases.^{77,78} Hereditary GC, that is, GC in the context of an associated germline mutation, accounts for 1%–5% of all cases of GC.⁷⁹ Family characteristics suggesting a hereditary predisposition include having several affected relatives, an autosomal dominant inheritance pattern, being affected at an early age and association with other extragastric cancers. Based on family and personal history, plus the histological type of the tumour (diffuse or intestinal), the patient should be assessed in terms of clinical diagnostic criteria for a situation with a hereditary basis associated with an increased risk of GC. If found, the corresponding germline genetic testing should be performed and endoscopic screening should be established based on the associated hereditary syndrome.⁷⁹ If a hereditary syndrome is ruled out, a diagnosis of familial GC is made if the

criteria for familial clustering are met. If they are not, the patient will be considered to have sporadic GC.

FDRs of a GC patient have an increased risk of developing this type of cancer. However, the magnitude of this risk varies by ethnic group, geographic region and degree of familial clustering. According to several case-control studies, the highest risk in FDRs is generally in the range of 1.5–3.5 times higher,⁸⁰ but it can be up to 10 times higher than the general population depending on the country.⁸¹ A recent meta-analysis of 32 studies assessing the risk of GC in FDRs revealed a 2.5 times higher risk of GC in FDRs compared to the general population. However, in the vast majority of studies, no genetic testing was performed to rule out a hereditary component.⁸² In Spain, there is one case-control study which included individuals with 1 FDR or 2 SDRs with GC, reporting an OR of 3.4 (95% CI: 1.9–6.0) compared to the control group.⁸³

One of the clinical situations involving higher risk is familial GC (FGC), in which familial clustering of GC of intestinal histology is found with no identified hereditary cause. The risk of GC increases with the number of family members affected. A study in 2010 showed that the risk of GC with an FDR was 2.7 (OR: 2.7; 95% CI: 1.7–4.3), with this risk increasing to 9.6 (OR: 9.6; 95% CI: 1.2–73.4) in individuals with two or more affected FDRs.⁸⁴ Another previous study also showed that having two or more FDRs carried a greater risk of GC than only one affected FDR (OR: 5.5; 95% CI: 3.0–10.2 vs OR: 1.7; 95% CI: 1.3–2.1) and that the risk was greater if the affected FDR was a sibling versus a parent (siblings: OR: 2.6; 95% CI: 1.8–3.7; parents: OR: 1.7; 95% CI: 1.3–2.2).⁸⁵

Members of the same family tend to have similar environmental factors such as socioeconomic status and dietary habits, and may even be infected with the same strain of *H. pylori*. Therefore, the results of studies aimed at assessing family history of GC as an independent risk factor for this type of cancer should be interpreted with caution. For example, a case-control study identified *H. pylori* infection and family history as independent risk factors for GC, although the two were positively related to each other. Thus, individuals with FDRs with GC and *H. pylori* had an eight times higher risk of GC (OR: 8.2; 95% CI: 2.2–30.4) and a 16 times higher risk of non-cardia GC (OR: 16.0; 95% CI: 3.9–66.4) than individuals with neither a family history nor *H. pylori* infection. However, it is impossible to analyse the risk of GC in individuals with a family history but without *H. pylori* infection, as 82% of the cohort with a family history were positive for *H. pylori*.⁸⁶

There is no scientific evidence or general consensus on the advisability of periodic gastroscopies or the interval between them. The most widely accepted recommendation at present is detection and eradication of *H. pylori* in FDRs of patients with GC.^{77,78,87} A recently published randomised control trial showed that, with a follow-up of 9.2 years, eradication of *H. pylori* reduces the risk of GC, both by intention to treat (eradication 1.2%, placebo 2.7%, HR: 0.45; 95% CI: 0.21–0.94) and by effective eradication (eradication 0.8%, non-eradication 2.9%, HR: 0.2; 95% CI: 0.1–0.7).⁸⁸

As regards endoscopic surveillance in familial GC, the recommendations are based on expert consensus. These recommendations are very heterogeneous, ranging from the recommendation not to do routine gastroscopies (within the framework of research only) to performing gastroscopies

annually or every three or five years. As previously mentioned, having a family history of GC carries an increased risk of *H. pylori* infection, gastric atrophy and IM, and there is evidence to suggest that gastric precancerous lesions in individuals with FDRs with GC have a higher risk of progression.⁸⁹ On that basis, some expert groups have suggested performing surveillance gastroscopies (with high-definition endoscopy and/or chromoendoscopy and taking targeted biopsies) every three years in patients with gastric atrophy or IM and a history of FDRs with GC.¹⁰

In individuals who meet criteria for familial GC, the expert consensus of the 2018 European Society of Digestive Oncology (ESDO) recommends annual screening with UGIE, similar to that used in the follow-up of individuals who meet criteria for hereditary diffuse GC with no identified germline mutation, from the age of 40 or five years before the age of onset in the youngest affected relative.⁹⁰ This examination must be performed according to the Cambridge protocol⁹¹: a) use of a high-definition endoscope; b) careful inspection for 30 min; c) gastric insufflation and deflation manoeuvres; d) use of mucolytics; e) biopsy of all mucosal abnormalities; f) serial biopsies (30 random biopsies are recommended, six from each region: antrum, incisura, corpus, fundus and cardia); and g) detection and eradication of *H. pylori*.

Expert opinion

As Spain is a low-risk country for GC, while solid scientific evidence is awaited, gastroscopies with biopsies according to the Sydney protocol and determination of *H. pylori* in biopsies will be recommended every three years¹⁰ from the age of 40, or five years before the age of onset in the youngest affected relative, exclusively in individuals from families with criteria for familial GC. In individuals with a family history of GC who do not meet the criteria for familial GC or a hereditary syndrome, testing for and eradication of *H. pylori* will be recommended. Finally, given the lack of scientific evidence and the highly heterogeneous follow-up of individuals with a family history of GC, it is essential that prospective studies be conducted in order to acquire a deeper understanding of GC risk based on family clustering and establish suitable screening and surveillance measures.

Management of patients with GCPLs

Eradication of *H. pylori* in patients with GCPLs

16. Should patients with atrophy or IM be tested and treated for *H. pylori*?

It is recommended that patients with gastric atrophy or intestinal metaplasia be tested and treated for H. pylori infection.

Low quality of evidence, strong recommendation in favour.

Agreement 4.64.

17. Should patients with dysplasia or carcinoma in situ be tested and treated for *H. pylori*?

It is recommended that patients be tested and treated for H. pylori infection following endoscopic resection of dysplasia or carcinoma in situ.

High quality of evidence, strong recommendation in favour.

Agreement 4.64.

Evidence

- **Advanced cancer.** A non-systematic search found no data to suggest any significant effect of *H. pylori* eradication on treatment or survival in patients with advanced GC.
- **Carcinoma in situ/HGD.** High-quality RCTs^{92,93} and several meta-analyses^{94–97} have been published with highly concordant results. These studies have shown that effective eradication of *H. pylori* reduces the development of metachronous lesions in approximately 50% of patients who have required endoscopic mucosal resection for EGC or carcinoma in situ.
- **IM/gastric atrophy and low-grade dysplasia (LGD).** In a technical review conducted by the American Gastroenterological Association (AGA) for clinical practice guidelines on IM, eradication of *H. pylori* reduced the risk of GC mortality (RR: 0.67; 95% CI: 0.38–1.17) and GC incidence (RR: 0.68; 95% CI: 0.48–0.96) both overall and specifically in patients with IM, although in the case of IM the reduction was not significant (RR 0.76; 95% CI: 0.36–1.61).⁹⁸ Recent RCTs also showed that eradication of *H. pylori* is associated with regression of IM at six and twelve years post-treatment in a significant percentage of patients.^{47,48} Those same studies also showed regression of LGD in some cases.^{47,48} By contrast, regression of HGD is very rare.⁴⁹

Expert opinion

Treatment of *H. pylori* has a clear protective effect against the development of metachronous lesions in patients who undergo endoscopic resection of high-grade gastric lesions. Although data on the efficacy of *H. pylori* infection treatment based on previous histology are limited, there are data suggesting that it may be effective in reducing the incidence of GC in patients with atrophy and, in particular, IM. The data are as follows:

- a) The published meta-analyses show a non-significant numerical trend in favour of treating *H. pylori*.
- b) Said treatment is effective in preventing metachronous lesions in patients who have received endoscopic treatment for cancerous lesions, and most of these patients have atrophy and/or IM.
- c) There is evidence that treating *H. pylori* could induce regression of advanced lesions in an undetermined percentage of patients.

Moreover, *H. pylori* treatment has very low morbidity and mortality rates, and the associated financial costs are low. In view of all the above, the quality of the evidence can be deemed low, but a strong recommendation in favour can be made.

Endoscopic surveillance and management of GCPLs

Gastric atrophy without metaplasia

18. Is endoscopic surveillance recommended in patients with gastric atrophy without IM?

Endoscopic surveillance is not recommended in patients with gastric atrophy without IM, regardless of extent.

Very low quality of evidence, strong recommendation against.

Agreement 4.8.

Evidence

The annual incidence of GC has been determined to be 0.1%–0.25% in patients with chronic atrophic gastritis.^{99,100} However, there is significant variability in the calculation of those figures. For example, in a Swedish study, the cumulative incidence at 20 years was approximately 2% in patients with chronic atrophic gastritis.¹⁰¹ A Japanese study found a higher cumulative incidence of GC at 5 years, reaching 1.9%–10% in patients with extensive chronic atrophic gastritis.¹⁰² A recent systematic review included 19,749 patients with atrophic gastritis, 261 of whom progressed to GC out of a total follow-up of 171,170 person-years. The incidence range for GC in this cohort was 0.53–15.24 per 1000 person-years. Most studies reported an incidence rate of 1.0–5.2 per 1000 person-years, and only two studies had more extreme results.¹⁰³ Specifically in Spain, González et al.¹⁰⁴ reported GC in 156 individuals with chronic atrophic gastritis over a follow-up period of 12 years.

Risk of GC increases with extent and degree of gastric atrophy; for example, an increased relative risk of GC of up to 5.76 has been reported in patients with severe atrophic gastritis of the corpus compared to those with minimal or no gastritis.^{100,105} Another Japanese study reported a relative risk of GC of 1.7 in patients with moderate atrophic gastritis and 4.9 in patients with severe atrophic gastritis, compared to individuals with no atrophy or mild atrophy.¹⁰⁶ In another study, the extent of gastric atrophy was related to the risk of GC detection: 5.33% in patients with atrophy in the entire stomach versus 0% and 0.25% in patients with atrophy limited to the antrum and atrophy in the incisura or corpus, respectively.¹⁰⁷

Finally, with regard to risk of dysplasia, in a retrospective study of patients with an undefined stage for dysplasia on baseline endoscopy and with OLGA staging, with a median follow-up of 31 months, no dysplasia was detected in any patients with OLGA 0/I/II, but six cases of dysplasia were detected in 25 patients with OLGA III/IV during said follow-up.¹⁰⁸

Expert opinion

The incidence of cancer in patients with extensive atrophy is not known, but may be in the region of 1 case per 1000 patients per year. One of the reasons for the difference in risk reported in the various studies is probably that some studies have not considered the extent or degree of atrophy in calculating the incidence of GC and/or dysplasia. Another important limitation is that the OLGA classification does not distinguish between metaplastic and non-metaplastic atrophy in the classification of atrophic gastritis, which makes interpretation of the results difficult. The diagnosis of atrophy on its own without taking IM into account has very high interobserver variability, making it a poor risk marker. Moreover, screening is not recommended as several of the key conditions established by regulatory agencies for recommending screening by are not met. There are no data on the acceptability of a screening programme and, above all, there is no evidence either in randomised studies or in observational studies that screening reduces the mortality rate. There are also no data on the potential impact on the

healthcare system, and there is no provision of resources for screening. In this context, screening is not recommended, pending data from future prospective studies. This reasoning is applicable to all GCPLs, but carries more weight in more difficult-to-characterise GCPLs, such as gastric atrophy, and in lower-risk situations, such as complete and/or localised IM.

Intestinal metaplasia

19. Is it necessary to repeat the UGIE after the initial diagnosis of IM?

A high-quality UGIE and staging by OLGIM at 6–12 months are recommended when IM is diagnosed in a low-quality UGIE.

Low quality of evidence, weak recommendation in favour.

Agreement 4.8.

20. Is endoscopic surveillance recommended in patients with IM?

Endoscopic surveillance is not recommended in patients with OLGIM I-II (focal IM).

Low quality of evidence, strong recommendation against.

Agreement: 4.75.

Not performing endoscopic surveillance is suggested in patients with OLGIM III-IV (extensive IM) without additional risk factors.

Very low quality of evidence, weak recommendation against.

Agreement 4.08.

Endoscopic surveillance every three years is suggested in patients with extensive IM (OLGIM III-IV) with incomplete IM or a family history of GC.

Very low quality of evidence, weak recommendation in favour.

Agreement 4.64.

Evidence

IM should be considered a risk factor for GC if it affects the mucosa of the corpus and the antrum. A total of ten cohort studies, including 25,912 patients with IM and a follow-up of 159,756 patient-years, assessed progression of IM to GC. The incidence density of GC was 12.4 (95% CI: 10.7–14.3) cases of GC per 10,000 patient-years, with a cumulative incidence of GC at three, five and ten years of 0.4, 1.1 and 1.6%, respectively.^{98,109}

As part of the AGA technical review to inform the clinical practice guidelines on IM, three factors that increased the risk of developing GC in patients with IM were identified.^{98,109} Having one or more FDRs with GC increased the risk 4.5 times (OR: 4.53; 95% CI: 1.33–15.46) in the four studies that analysed this factor compared to those with no FDRs with GC. Seven studies evaluated the risk of developing GC based on the histological type of IM. Incomplete IM was associated with an increased risk of GC during a follow-up of 3–12.8 years (RR: 3.33; 95% CI: 1.96–5.64). With regard to extent of IM, only two studies provided information for assessing risk during follow-up. Extensive IM was associated with a non-significant increase in the risk of GC (RR: 2.07; 95% CI: 0.97–4.42). These data are consistent with those from various case-control studies in which an associa-

tion was found between extensive IM (OLGIM III/IV) and GC detection.^{110–113}

Another risk factor widely associated with an increased risk of GC, pernicious anaemia, was assessed in this review. Only one study that evaluated the prevalence of IM in pernicious anaemia was identified. Although the incidence of IM was high, 88.9% (95% CI: 70.8–96.6%), the study had multiple limitations: sample size (27 patients), diagnostic criteria and potential selection biases. Therefore, this document does not make a separate recommendation for patients with pernicious anaemia/autoimmune gastritis and proposes establishing the indication for surveillance in these patients in the same way as in the general population, based on the histological lesion and additional risk factors.^{98,109}

In Europe, a recent Swedish study that analysed more than 400,000 patients concluded that IM (regardless of the degree of extension) significantly increases the risk of GC. This study showed that a second UGIE with biopsies can have significant prognostic value, as GCPL regression (IM no longer detected) can occur during follow-up, and this is associated with a lower risk of progression to GC.¹⁰¹

However, the prevalence of focal IM in the European population is around 16%–18%, and it seems unreasonable to consider surveillance of these patients.¹¹⁴ Also, although the same authors believed that IM could increase the risk of GC compared to the absence of IM or even just atrophy, the risk seems too low to justify surveillance.⁴²

Once again, as mentioned in the case of gastric mucosal atrophy, there are no RCTs on the benefits or risks of endoscopic surveillance in patients with GCPLs.^{98,109} The evidence comes from non-experimental studies with selection biases and different diagnostic criteria and surveillance schedules.^{40,110,115} One cohort study compared the risk of detection of GC and stage at diagnosis between a group of 166 individuals with diagnoses of IM, dysplasia, ulcers or polyps and endoscopic surveillance for 10 years, and a group of 1753 patients with no surveillance. In the group of patients in the surveillance programme, there was a higher percentage of cases of GC diagnosed in early stages and an increase in 5-year survival among patients who underwent surgery.¹¹⁵ However, most of the cancers were detected during monitoring of suspected gastric ulcers and/or in the first year of follow-up, suggesting that many of the lesions were incipient cancers undiagnosed in the index UGIE. Therefore, the results are not applicable to screening. In the most recently published study, 279 patients with GCPLs had at least one surveillance endoscopy during a mean follow-up interval of 57 months. Four cases with HGD or GC were detected, all in individuals with OLGIM III-IV.¹¹⁰ Another recently published retrospective study analysed the factors associated with the development of GC in 332 patients with atrophic gastritis and a mean follow-up of 9.2 years in an Asian population. During the follow-up period, 16 GC were detected with an incidence of 0.53/1000 patient-years. This study corroborated that the factors associated with the risk of GC detection are the extent of the GCPLs and *H. pylori* infection. Overall, endoscopic surveillance did not reduce the risk of GC. However, in individuals with extensive GCPLs, a multivariate analysis suggested that endoscopic surveillance at 2–3 year intervals reduced the risk of GC (HR: 0.01; 95% CI: 0.001–0.34). The limitations of this study were its lack of determination of GCPL extent, its retrospective

nature and the fact that it included different surveillance periods.¹¹⁶

Expert opinion

The increase in the risk of GC associated with IM is limited. In patients with GCPLs, the risk of developing GC is confined mainly to patients with dysplasia or extensive IM (OLGIM III-IV). In the case of extensive IM, this risk increases when there are other associated risk factors such as incomplete IM or a family history of GC. However, there is no evidence linking autoimmune atrophic gastritis to a higher risk of GC detection in IM.^{98,109,114} The risk of GC in patients with focal IM (OLGIM I-II) is very low — in fact, it is not significantly higher than in the general population. As indicated in the AGA technical review,^{98,109} there is no quality evidence to recommend endoscopic surveillance in patients with IM. Prospective studies are required to evaluate the effect of endoscopic surveillance on the incidence of GC in these patients.

Furthermore, the conditions required by regulatory agencies are not met. There are no data on the acceptability of a screening programme or on the potential impact on the healthcare system, and there is no provision of resources for screening. In this context, screening is not recommended, pending data from future prospective studies.

The panel agrees that research in this field is needed. Therefore, it is recommended that the risks and benefits of screening be discussed with patients with extensive IM, and that the non-recommendation and the lack of evidence on efficacy be made clear. Given the low quality of the evidence, screening would be reasonable if the patient showed a preference in this regard. Both those who agree and those who do not should be included in a registry that evaluates the effectiveness of long-term screening. Outside of clinical research, there is no scientific evidence to recommend screening.

However, in patients with several risk factors (extensive IM associated with incomplete IM and/or a family history of GC), offering endoscopic surveillance has been considered reasonable, provided the unproven reduction in the risk of GC versus the risks and discomfort associated with this type of screening are discussed with the patient. This is intended, first, to offer screening to patients with a higher potential risk and, second, to have data on the potential usefulness of screening in Spain in these higher-risk patients, which will enable evaluation of its effectiveness.

There is no information on the effect of the risk of autoimmune origin on the risk of developing GC in IM associated with pernicious anaemia. Consequently, we do not recommend specific surveillance in these patients. Based on expert opinion, some consensus statements have suggested that an interval of 2–3 years may be suitable in patients with extensive IM who require endoscopic surveillance. In our case, in view of the lack of evidence, it was decided to recommend the use of the same criteria for follow-up proposed for patients with GCPLs.

Dysplasia and carcinoma in situ

21. Is endoscopic resection recommended in patients with dysplastic lesions?

Resection of visible lesions with dysplasia is recommended for accurate histological diagnosis.

High quality of evidence, strong recommendation in favour.

Agreement 4.83.

22. Is a repeat endoscopy recommended following a diagnosis of dysplasia without visible lesions?

Quality endoscopy is recommended for reassessment within 6 months following a diagnosis of dysplasia of any grade.

Very low quality of evidence, strong recommendation in favour.

Agreement 4.66.

Evidence

LGD has traditionally been described as having a significant risk of progression to GC. However, no studies have evaluated this risk in a large number of patients, and those that have been conducted have included LGD and moderate dysplasia in the same group. Furthermore, these studies feature no information on whether the lesions were visible or invisible. For example, a study conducted in the United States that included 141 individuals with LGD under endoscopic surveillance reported an incidence of GC of 7.7/1000 person-years, with a relative risk of 25.6 (95% CI: 9.4–55.7) and a median time of 2.6 years for progression to GC.¹¹⁷ Similarly, a cohort study conducted in the Netherlands reported an annual risk of progression from mild or moderate dysplasia to GC of 0.6%.¹⁰⁰ However, these results were not confirmed in a more recent study, also conducted in the Netherlands, in which none of the prospectively followed-up cases with LGD progressed to HGD or GC after a mean follow-up period of 4.7 years.¹¹⁰

No studies have examined whether endoscopic resection of visible lesions with LGD reduces the incidence or mortality rates of GC and/or HGD compared to no treatment.¹⁰⁰ In any event, the finding of dysplasia is a risk marker for GC. In some studies,¹⁰⁰ a high number of patients with GC were detected in the first year of follow-up of patients with HGD; therefore, a short-term reassessment is recommended in these patients. Those with mild or moderate dysplasia should also be reassessed, but the interval is not well defined and could be from six months to a year. LGD is also a potential sign of malignancy, as many biopsies of visible lesions may be negative for dysplasia and obscure a true neoplasm due to a sampling error.¹¹⁸ A Western series that studied specimens from submucosal endoscopic dissections found that histological staging with an upward trend occurs after endoscopic resection (ER) in 33% of lesions.¹¹⁹ Similarly, an Eastern study that analysed 1850 lesions detected a discrepancy of 32% between endoscopic biopsies and ER specimens.¹¹⁸ A meta-analysis that specifically investigated the possibility of upward re-staging of LGD after ER showed that this occurs in 25% of lesions, with 7% being definitively determined to be GC.¹²⁰

Expert opinion

The diagnosis of LGD is problematic, as biopsies have been reported to under-stage dysplasia, and many visible LGD lesions are actually already malignant.¹²¹ In a meta-analysis that analysed changes in LGD staging after endoscopic

resection, reclassification to more advanced stages was reported in up to 25% of the lesions, 7% of which were already malignant.¹²⁰ Detailed examination of the lesions with magnification endoscopy and virtual chromoendoscopy such as narrow-band imaging enables identification of certain characteristics suggestive of worse histology,¹²² but this technique is not widely available in Spain. For that reason, the recent “Management of epithelial precancerous conditions and lesions in the stomach” (MAPS II) guidelines recommend that all visible lesions (including those with LGD) should be resected.¹⁰

23. What type of endoscopic follow-up should be done following resection of a lesion with dysplasia?

It is suggested that endoscopic surveillance be done annually for 2 years and according to baseline risk thereafter following endoscopic resection of LGD.

Very low quality of evidence, weak recommendation in favour.

Agreement 4.41.

Following resection of HGD or carcinoma in situ, it is suggested that endoscopic surveillance be done every six months for the first year, then annually for three years and according to baseline risk thereafter.

Very low quality of evidence, weak recommendation in favour.

Agreement 4.42.

Evidence

The prevalence of dysplasia (in general) in routine endoscopies ranges from 0.5% to 3.75% in Western countries and from 9% to 20% in regions with a high incidence of GC, such as Colombia and China.¹²³ There is evidence to suggest that patients with HGD have a high risk of progression to cancer¹¹⁰ and of synchronous neoplasia.¹²⁴ A recent cohort study demonstrated that HGD was an independent risk factor for GC (HR: 18.8; 95% CI: 9.0–39.5). The standardised incidence of GC was 2.0 (95% CI: 1.5–2.6) in the subgroup of individuals without dysplasia and 35.2 (95% CI: 15.2–69.4) in the subgroup with HGD.¹²⁵ However, the real risk of progression from dysplasia to cancer is not well defined due to the difficulty of finding prospective, well-designed studies with proper biopsy that analyse the natural history of dysplasia. The rate of HGD becoming malignant ranges from 25% to 85% with a time interval between 4 and 48 months, depending on the study.¹²⁶ For example, a Dutch study reported that 25% of patients diagnosed with HGD developed GC within the following year.¹⁰⁰ An important factor in the variability of the incidence of GC secondary to gastric HGD is the high rate of discrepancy in the diagnosis of HGD. Although biopsy is the standard method for HGD diagnosis, malignant lesions are underdiagnosed in 40%–66% of cases compared to the analysis following resection.^{127–129}

Moreover, after curative ER of a gastric neoplasm, other lesions may appear in the gastroscopies performed during follow-up. These lesions may be of new onset, not detected in previous gastroscopies or the result of the progression of previously invisible lesions that were already present in a preclinical phase. As this distinction is often difficult to make, new (metachronous) lesions are defined by consensus as those that appear at a distance from the original cancer at least one year after ER.¹³⁰ Lesions that appear during the

first year are therefore considered to be synchronous cancers not detected during the initial gastroscopy. The data on the overall incidence of metachronous GC after ER show a great deal of variability in the literature, with figures ranging from 2.7% to 15.6%.¹³⁰

A retrospective study that included 947 patients assessed the incidence of gastric cancer after ER of EGC with a median follow-up of 2.3 years.¹³¹ The incidence of GC was 14.4 cases per 1000 person-years after LGD resection and 18.4 cases per 1000 person-years after resection of HGD and/or EGC, without statistically significant differences. There were also no differences in the cumulative incidence of gastric cancer and an increased risk was only identified in the detection of invasive GC in the LGD group. In another retrospective study, published by Cho et al.,¹³² 2779 patients with 2981 lesions (518 cases of HGD and 2463 cases of EGC) were included with a median follow-up of 42 months. The cumulative incidence of metachronous lesions at five and ten years was 4.6% and 10.5%, respectively, and the annual incidence was 0.9%, with no statistically significant differences between patients with HGD and those with EGC. The annual incidence of metachronous lesions was 1.02% in the HGD group and 0.88% in the EGC group. Again, one of the most important limitations of this study was the high percentage of dropouts from follow-up during the first year. Another retrospective, single-centre study of Korean origin¹³³ reported the incidence of metachronous cancers in 641 patients who underwent ER for dysplastic gastric lesions (84% LGD and 16% HGD) after a median follow-up of 29 months. The annual incidence of metachronous lesions was 1.26%, and the cumulative incidence of metachronous cancers five years after ER of dysplastic lesions was 31%. In the multivariate analysis, male sex (OR 2.3; 95% CI: 1.3–4.2), IM (OR 1.9; 95% CI: 1.2–3.0) and HGD (OR 2.7; 95% CI: 1.16–6.26) were independent risk factors for the development of metachronous lesions. Finally, a recent retrospective study, which included 316 endoscopically resected gastric cancers, also evaluated the risk of metachronous lesions based on three histological groups — LGD, HGD and EGC — over a median follow-up of 4.2 years.¹³⁴ The incidence of GC after ER was 15.2 cases per 1000 person-years in the LGD group, 18.5 cases per 1000 person-years in the HGD group and 20.9 cases per 1000 person-years in the EGC group. The incidence of metachronous cancers was 28.6, 45.7 and 39.7 cases per 1000 person-years in the LGD, HGD and EGC groups, respectively, with no statistically significant differences between the different groups. In the multivariate analysis, the only independent risk factor for the development of cancers or metachronous GC was male sex.

Expert opinion

The available studies have multiple limitations in both design and follow-up. Also, the data come exclusively from the Asian population, so extrapolation to a Western environment entails a certain likelihood of bias. However, the figures for incidence of metachronous cancers are consistent across the different studies analysed. Overall, the rate of onset of new lesions following ER of lesions with HGD/intraepithelial cancer is very high, with 10–20 cases per 1000 person-years. This enables recommendation of

close monitoring, particularly following resection of HGD or carcinoma in situ.

24. What type of endoscopic follow-up should be done in dysplasia without visible lesions?

With a diagnosis of dysplasia without visible lesions after a quality UGIE with chromoendoscopy, it is suggested that endoscopic follow-up be done at 6 months (HGD) to 12 months (LGD).

Very low quality of evidence, weak recommendation in favour.

Agreement 4.46.

Evidence

In a 2011 prospective study by Simone et al.,¹³⁵ three expert endoscopists reassessed 20 patients with a diagnosis of invisible dysplasia. The examinations were performed with high-definition endoscopes, mucolytic lavage and virtual or conventional chromoendoscopy. A total of 18 visible lesions were identified: 13 cases of high-grade dysplasia and 5 cases of carcinoma. In 2016, Yep-Gamarra et al. conducted a prospective study in Spain¹³⁶ that included 50 patients with a histological diagnosis of a pre-malignant lesion in the previous 6 months. The authors performed a protocolised gastroscopy with chromoendoscopy with indigo carmine and acetic acid, resulting in a higher percentage of patients diagnosed with dysplasia and visible lesions.

Expert opinion

Detection of dysplasia in random biopsies is not uncommon. As set out in this document, numerous factors can contribute to the failure to detect a lesion in conventional gastroscopy. Although the evidence supporting this recommendation comes from observational studies, we believe that a quality gastroscopy focused on the detection of dysplastic lesions is the fundamental step for the problem of invisible dysplasia, as it enables identification of resectable lesions in a significant percentage of patients.

No studies evaluating the optimal follow-up interval in patients with invisible dysplasia after quality gastroscopy were found. Considering that the presence of dysplasia is a factor for the development of gastric carcinoma¹³⁷ and the risk of not having detected an existing lesion, we believe high-quality endoscopic reassessment is advisable within a maximum of 6–12 months, depending on whether the patient has HGD or LGD.¹⁰

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Conflicts of interest

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References

1. World Health Organization [accessed 23 May 2020]. Cancer Today. International Agency for Research on Cancer. Available from; 2020 <https://gco.iarc.fr/today/home>
2. Jaume Galceran A, Galcerán J, Ameijide A, Carulla M, Bonet RP. Estimaciones de la incidencia y la supervivencia del cáncer en España y su situación en Europa. Redecan. 2014.
3. Lee Y-C, Chiang T-H, Chou C-K. Association between helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology. 2016;150:1113-1124.e5.
4. Seta T, Takahashi Y, Noguchi Y, Shikata S, Sakai T, Sakai K, et al. Effectiveness of Helicobacter pylori eradication in the prevention of primary gastric cancer in healthy asymptomatic people: a systematic review and meta-analysis comparing risk ratio with risk difference. PLoS One. 2017;12:e0183321.
5. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ. 2014;348:g3174.
6. Ford AC, Yuan Y, Forman D, Hunt R, Moayyedi P. Helicobacter pylori eradication for the prevention of gastric neoplasia. Cochrane database Syst Rev. 2020;7. CD005583.
7. Gisbert JP, Calvet X, Bermejo F, Boixeda D, Bory F, Bujanda L, et al. III Spanish Consensus Conference on Helicobacter pylori infection. Gastroenterol Hepatol. 2013;36:340-74.
8. Gisbert JP, Molina-Infante J, Amador J, Bermejo F, Bujanda L, Calvet X, et al. IV Spanish Consensus Conference on Helicobacter pylori infection treatment. Gastroenterol Hepatol. 2016;39:697-721.
9. Correa P. A human model of gastric carcinogenesis. Cancer Res. 1988;48:3554-60.
10. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Port. Endoscopy. 2019;51:365-88.
11. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64:380-2.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377-81.
13. Rugge M, Correa P, Dixon MF, Fiocca R, Hattori T, Lechago J. Gastric mucosal atrophy: interobserver consistency using new criteria for classification and grading. Aliment Pharmacol Ther. 2002;16:1249-59.
14. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996;20:1161-81.
15. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours. iarc, ed; 2010.
16. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000;47:251-5.
17. Rugge M, Correa P, Dixon MF, Hattori T, Leandro G, Lewin K, et al. Gastric dysplasia: the Padova international classification. Am. J. Surg. Pathol. 2000;24:167-76.

18. Goo JJ, Choi CW, Kang DH, Kim HW, Park SB, Cho M, et al. Risk factors associated with diagnostic discrepancy of gastric indefinite neoplasia: Who need en bloc resection? *Surg Endosc*. 2015;29:3761–7.
19. Leoz M.L., Sánchez A., Carballal S., Ruano L, Ocaña T, Pellisé M, et al. Hereditary gastric and pancreatic cancer predisposition syndromes. *Gastroenterol. Hepatol*. 39:481–493.
20. Bisschops R, Areia M, Coron E, Dobru D, Kaskas B, Kuvaev R, et al. Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy*. 2016;48:843–64.
21. Beg S, Ragunath K, Wyman A, Banks M, Trudgill N, Pritchard DM, et al. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS). *Gut*. 2017;66:1886–99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28821598>
22. Teh JL, Tan JR, Lau LJF, Saxena N, Salim A, Tay A, et al. Longer examination time improves detection of gastric cancer during diagnostic upper gastrointestinal endoscopy. *Clin Gastroenterol Hepatol*. 2015;13:480–487.e2.
23. Fock KM, Ang TL. Epidemiology of *Helicobacter pylori* infection and gastric cancer in Asia. *J. Gastroenterol. Hepatol*. 2010;25:479–86.
24. Wilson JGG (WHO, ed.). Geneva Principles and practice of screening for disease. World Health Organization Public Health Paper 34; 1968.
25. UK National Screening Committee (UK NSC). Criteria for appraising the viability, effectiveness and appropriateness of a screening programme Updated 23 October 2015; 2015. Available at: <https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme> [Accessed June 2, 2020].
26. Alfons S, Márquez S, Meléndez I, Núñez D, González A, Cabanas C, et al. Documento marco sobre cribado poblacional; 2013.
27. Anon. Instituto Nacional de Estadística. Available at: www.ine.es [Accessed December 19, 2017].
28. Rodríguez-de-Santiago E, Frazzoni L, Fuccio L, van Hooft JE, Ponchon T, Hassan C, et al. Digestive findings that do not require endoscopic surveillance – Reducing the burden of care: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. 2020.
29. Rugge M, Genta RM, OLGA Group. Staging gastritis: an international proposal. *Gastroenterology*. 2005;129:1807–8.
30. Capelle LG, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, et al. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointest Endosc*. 2010;71:1150–8.
31. Rugge M, Meggio A, Pennelli G, Pisciole F, Giacomelli L, De Pretis G, et al. Gastritis staging in clinical practice: the OLGA staging system. *Gut*. 2007;56:631–6.
32. Satoh K, Osawa H, Yoshizawa M, Nakano H, Hirasawa T, Kihira K, et al. Assessment of atrophic gastritis using the OLGA system. *Helicobacter*. 2008;13:225–9.
33. Rugge M, de Boni M, Pennelli G, de Bona M, Giacomelli L, Fassan M, et al. Gastritis OLGA-staging and gastric cancer risk: a twelve-year clinico-pathological follow-up study. *Aliment Pharmacol Ther*. 2010;31:1104–11.
34. den Hoed CM, Holster IL, Capelle LG, de Vries AC, den Hartog B, Ter Borg F, et al. Follow-up of premalignant lesions in patients at risk for progression to gastric cancer. *Endoscopy*. 2013;45:249–56.
35. Offerhaus GJ, Price AB, Haot J, ten Kate FJ, Sipponen P, Fiocca R, et al. Observer agreement on the grading of gastric atrophy. *Histopathology*. 1999;34:320–5.
36. Chen XY, van der Hulst RW, Bruno MJ, van der Ende A, Xiao SD, Tytgat GN, et al. Interobserver variation in the histopathological scoring of *Helicobacter pylori* related gastritis. *J Clin Pathol*. 1999;52:612–5.
37. Vukobrat-Bijedić Z, Radović S, Husić-Selimović A, Gornjakovic S. Incomplete intestinal metaplasia as an indicator for early detection of gastric carcinoma in the events of *Helicobacter pylori* positive chronic atrophic gastritis. *Bosn J Basic Med Sci*. 2006;6:48–53.
38. Filipe MI, Muñoz N, Matko I, Kato I, Pompe-Kirn V, Jutersek A, et al. Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. *Int J Cancer*. 1994;57:324–9.
39. Craanen ME, Blok P, Dekker W, Ferwerda J, Tytgat GN. Prevalence of subtypes of intestinal metaplasia in gastric antral mucosa. *Dig. Dis. Sci*. 1991;36:1529–36.
40. Rokkas T, Filipe MI, Sladen GE. Detection of an increased incidence of early gastric cancer in patients with intestinal metaplasia type III who are closely followed up. *Gut*. 1991;32:1110–3.
41. González CA, Pardo ML, Liso JMR, Alonso P, Bonet C, García RM, et al. Gastric cancer occurrence in preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. *Int J Cancer*. 2010;127:2654–60.
42. Mera RM, Bravo LE, Camargo MC, Bravo JC, Delgado AG, Romero-Gallo J, et al. Dynamics of *Helicobacter pylori* infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up of an eradication trial. *Gut*. 2018;67:1239–46.
43. Cassaro M, Rugge M, Gutierrez O, Leandro G, Graham DY, Genta RM. Topographic patterns of intestinal metaplasia and gastric cancer. *Am J Gastroenterol*. 2000;95:1431–8.
44. Raftopoulos SC, Kumarasinghe P, de Boer B, Iacobelli J, Kontorinis N, Fermoye S, et al. Gastric intraepithelial neoplasia in a Western population. *Eur J Gastroenterol Hepatol*. 2012;24:48–54.
45. de Vries AC, Kuipers EJ. Review article: *Helicobacter pylori* eradication for the prevention of gastric cancer. *Aliment. Pharmacol. Ther*. 2007;26 Suppl 2:25–35.
46. Wang J, X.u L, Shi R, Huang X, L.i SWH, Huang Z, et al. Gastric atrophy and intestinal metaplasia before and after *Helicobacter pylori* eradication: a meta-analysis. *Digestion*. 2011;83:253–60.
47. Mera R, Fontham ETH, Bravo LE, Bravo JC, Piazzuelo MB, Camargo MC, et al. Long term follow up of patients treated for *Helicobacter pylori* infection. *Gut*. 2005;54:1536–40.
48. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst*. 2000;92:1881–8.
49. Rugge M, Capelle LG, Cappellesso R, Nitti D, Kuipers EJ, et al. Precancerous lesions in the stomach: from biology to clinical patient management. *Best Pract Res Clin Gastroenterol*. 2013;27:205–23.
50. Song H, Zhu J, L.u D. Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. *Cochrane database Syst Rev*. 2014. CD010623.
51. Hagiwara T, Mukaisho K-I, Nakayama T, Sugihara H, Hattori T. Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with *Helicobacter pylori*. *Gut*. 2011;60:624–30.
52. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review

- of the current evidence. *Therap. Adv Gastroenterol.* 2019;12:1756284819834511.
53. Nasser SC, Slim M, Nassif JG, Nasser SM. Influence of proton pump inhibitors on gastritis diagnosis and pathologic gastric changes. *World J Gastroenterol.* 2015;21:4599–606.
 54. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, et al. Management of *Helicobacter pylori* infection-the Maastricht IV/ Florence Consensus Report. *Gut.* 2012;61:646–64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22491499>
 55. Kwon MJ, Kang HS, Kim HT, Choo JW, Lee BH, Hong SE, et al. Treatment for gastric 'indefinite for neoplasm/dysplasia' lesions based on predictive factors. *World J Gastroenterol.* 2019;25:469–84.
 56. Nam HS, Choi CW, Kim SJ, Kang DH, Kim HW, Park SB, et al. Endoscopic submucosal dissection for gastric indefinite for neoplasia: which lesions should be resected? *Surg Endosc.* 2019;33:3976–83.
 57. Kim JM, Sohn JH, Cho M-Y, Kim WH, Chang HK, Jung ES, et al. Inter-observer reproducibility in the pathologic diagnosis of gastric intraepithelial neoplasia and early carcinoma in endoscopic submucosal dissection specimens: a multi-center study. *Cancer Res. Treat.* 2019;51:1568–77.
 58. Doorakkers E, Lagergren J, Engstrand L, Brusselsaers N. Eradication of *Helicobacter pylori* and gastric cancer: a systematic review and meta-analysis of cohort studies. *J Natl Cancer Inst.* 2016;108.
 59. Areia M, Carvalho R, Cadime AT, Rocha Gonçalves F, Dinis-Ribeiro M. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. *Helicobacter.* 2013;18:325–37.
 60. Lee Y-C, Chiang T-H, Liou J-M, Chen H-H, W.u M-S, Graham DY. Mass eradication of *helicobacter pylori* to prevent gastric cancer: theoretical and practical considerations. *Gut Liver.* 2016;10:12–26.
 61. Macenlle García R, Gayoso Diz P, Sueiro Benavides RA, Sueiro Benavides RA, Fernández Seara J. Prevalence of *Helicobacter pylori* infection in the general adult population of the province of Ourense. *Rev Esp Enferm Dig.* 2006;98:241–8.
 62. Geboes K, Dekker W, Mulder CJ, Nusteling K, Dutch Study Group. Long-term lansoprazole treatment for gastroesophageal reflux disease: clinical efficacy and influence on gastric mucosa. *Aliment Pharmacol Ther.* 2001;15:1819–26.
 63. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, et al. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med.* 1996;334:1018–22.
 64. Lundell L, Vieth M, Gibson F, Nagy P, Kahrilas PJ. Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology. *Aliment Pharmacol Ther.* 2015;42:649–63.
 65. Huang Y, Yu J, Kang W, Ma Z, Ye X, Tian S, et al. Significance of serum pepsinogens as a biomarker for gastric cancer and atrophic gastritis screening: a systematic review and meta-analysis. *PLoS One.* 2015;10:e0142080.
 66. Bang CS, Lee JJ, Baik GH. Prediction of chronic atrophic gastritis and gastric neoplasms by serum pepsinogen assay: a systematic review and meta-analysis of diagnostic test accuracy. *J Clin Med.* 2019;8.
 67. Cai Q, Zhu C, Yuan Y, Feng Q, Feng Y, Hao Y, et al. Development and validation of a prediction rule for estimating gastric cancer risk in the Chinese high-risk population: a nationwide multicentre study. *Gut.* 2019;68:1576–87.
 68. Marques-Silva L, Areia M, Elvas L, Dinis-Ribeiro M. Prevalence of gastric precancerous conditions: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2014;26:378–87.
 69. McNicholl AG, Forné M, Barrio J, De la Caba C, González B, Rivera R, et al. Accuracy of GastroPanel for the diagnosis of atrophic gastritis. *Eur J Gastroenterol Hepatol.* 2014;26:941–8.
 70. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol.* 2008;38:259–67.
 71. Riecken B, Pfeiffer R, Ma JL, Jin ML, Li JY, Liu WD, et al. No impact of repeated endoscopic screens on gastric cancer mortality in a prospectively followed Chinese population at high risk. *Prev Med (Baltim).* 2002;34:22–8.
 72. Hamashima C, Ogoshi K, Okamoto M, Shabana M, Kishimoto T, Fukao A, et al. A community-based, case-control study evaluating mortality reduction from gastric cancer by endoscopic screening in Japan. *PLoS One.* 2013;8:e79088.
 73. Jun JK, Choi KS, Lee H-Y, Suh M, Park B, Song SH, et al. Effectiveness of the Korean National Cancer Screening Program in reducing gastric cancer mortality. *Gastroenterology.* 2017;152:1319–1328.e7.
 74. Saumoy M, Schneider Y, Shen N, Kahaleh M, Sharaiha RZ, Shah SC, et al. Cost effectiveness of gastric cancer screening according to race and ethnicity. *Gastroenterology.* 2018;155:648–60.
 75. Aragonés N, Izarzugaza MI, Ramos M, Chirlaque MD, Almar E, Martínez C, et al. Trends in oesophago-gastric cancer incidence in Spain: analysis by subsite and histology. *Ann Oncol Off J Eur Soc Med Oncol.* 2010;21 Suppl 3, iii69–75.
 76. Aragonés N, Pérez-Gómez B, Pollán M, Ramis R, Vidal E, Lope V, et al. The striking geographical pattern of gastric cancer mortality in Spain: environmental hypotheses revisited. *BMC Cancer.* 2009;9:316.
 77. Corso G, Roncalli F, Marrelli D, et al. History, pathogenesis, and management of familial gastric cancer: original study of John XXIII's family. *Biomed Res. Int.* 2013;2013:385132.
 78. Kluijdt I, Sijmons RH, Hoogerbrugge N, Carneiro F, Roviello F. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. *Fam. Cancer.* 2012;11:363–9.
 79. Carneiro F. Hereditary gastric cancer. *Pathologie.* 2012;33 Suppl 2:231–4.
 80. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst.* 1994;86:1600–8.
 81. Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. *Br J Cancer.* 2010;102:237–42.
 82. Yaghoobi M, McNabb-Baltar J, Bijarchi R, Hunt RH. What is the quantitative risk of gastric cancer in the first-degree relatives of patients? A meta-analysis. *World J Gastroenterol.* 2017;23:2435–42.
 83. García-González MA, Lanás A, Quintero E, Nicolás D, Parra-Blanco A, Strunk M, et al. Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: a Nationwide Multicenter Study in Spain. *Am J Gastroenterol.* 2007;102:1878–92.
 84. Shin CM, Kim N, Yang HJ, Cho S-I, Lee HS, Kim JS, et al. Stomach cancer risk in gastric cancer relatives: interaction between *Helicobacter pylori* infection and family history of gastric cancer for the risk of stomach cancer. *J Clin Gastroenterol.* 2010;44:e34–9.
 85. Palli D., Galli M., Caporaso N.E., Cipriani F, Decarli A, Saieva C, et al. Family history and risk of stomach cancer in Italy. *Cancer Epidemiol. Biomarkers Prev.* 3:15–18.
 86. Brenner H, Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dharm G. Individual and joint contribution of family history and *Helicobacter pylori* infection to the risk of gastric carcinoma. *Cancer.* 2000;88:274–9.

87. Choi YJ, Kim N. Gastric cancer and family history. *Korean J Intern Med.* 2016;31:1042–53.
88. Choi IJ, Kim CG, Lee JY, Kim Y, Kook MC, Park B, et al. Family history of gastric cancer and *Helicobacter pylori* treatment. *N Engl J Med.* 2020;382:427–36.
89. Reddy KM, Chang JI, Shi JM, Wu BU. Risk of gastric cancer among patients with intestinal metaplasia of the stomach in a US integrated health care system. *Clin Gastroenterol Hepatol.* 2016;14:1420–5.
90. Vangala DB, Cauchin E, Balmaña J, Wyrwicz L, van Cutsem E, Güller U, et al. Screening and surveillance in hereditary gastrointestinal cancers: Recommendations from the European Society of Digestive Oncology (ESDO) expert discussion at the 20th European Society for Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer. *Eur J Cancer.* 2018;104:91–103.
91. Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet.* 2010;47:436–44.
92. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet (London, England).* 2008;372:392–7.
93. Choi IJ, Kook M-C, Kim Y-I, Cho S-J, Lee JY, Kim CG, et al. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. *N Engl J Med.* 2018;378:1085–95.
94. Zhao B, Zhang J, Mei D, Luo R, Lu H, Xu H, et al. Does *Helicobacter pylori* eradication reduce the incidence of metachronous gastric cancer after curative endoscopic resection of early gastric cancer: a systematic review and meta-analysis. *J Clin Gastroenterol.* 2019.
95. Yoon SB, Park JM, Lim C-H, Cho YK, Choi M-G. Effect of *Helicobacter pylori* eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. *Helicobacter.* 2014;19:243–8.
96. Jung DH, Kim J-H, Chung HS, Park JC, Shin SK, Lee SK, et al. *Helicobacter pylori* eradication on the prevention of metachronous lesions after endoscopic resection of gastric neoplasm: a meta-analysis. *PLoS One.* 2015;10:e0124725.
97. Xiao S, Li S, Zhou L, Jiang W, Liu J. *Helicobacter pylori* status and risks of metachronous recurrence after endoscopic resection of early gastric cancer: a systematic review and meta-analysis. *J Gastroenterol.* 2019;54:226–37.
98. Gawron AJ, Shah SC, Altayar O, Davitkov P, Morgan D, Turner K, et al. AGA technical review on gastric intestinal metaplasia - natural history and clinical outcomes. *Gastroenterology.* 2019.
99. Lahner E, Esposito G, Pillozzi E, Purchiaroni F, Corleto VD, Di Giulio E, et al. Occurrence of gastric cancer and carcinoids in atrophic gastritis during prospective long-term follow up. *Scand J Gastroenterol.* 2015;50:856–65.
100. de Vries AC, van Grieken NCT, Looman CWN, Casparie MK, deVries E, Meijer GA, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology.* 2008;134:945–52.
101. Song H, Ekheden IG, Zheng Z, Ericsson J, Nyrén O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. *BMJ.* 2015;351:h3867.
102. Shichijo S, Hirata Y, Niihara R, Hayakawa Y, Yamada A, Ushiku T, et al. Histologic intestinal metaplasia and endoscopic atrophy are predictors of gastric cancer development after *Helicobacter pylori* eradication. *Gastrointest Endosc.* 2016;84:618–24.
103. Spence AD, Cardwell CR, McMenamin UC, Hicks BM, Johnston BT, Murray LJ, et al. Adenocarcinoma risk in gastric atrophy and intestinal metaplasia: a systematic review. *BMC Gastroenterol.* 2017;17:157.
104. González CA, Sanz-Anquela JM, Companioni O, Bonet C, Berdasco M, López C, et al. Incomplete type of intestinal metaplasia has the highest risk to progress to gastric cancer: results of the Spanish follow-up multicenter study. *J Gastroenterol Hepatol.* 2016;31:953–8.
105. Tatsuta M, Iishi H, Nakaizumi A, Okuda S, Taniguchi H, Hiyama T, et al. Fundal atrophic gastritis as a risk factor for gastric cancer. *Int J Cancer.* 1993;53:70–4.
106. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med.* 2001;345:784–9.
107. Masuyama H, Yoshitake N, Sasai T, Nakamura T, Masuyama A, Zuiki T, et al. Relationship between the degree of endoscopic atrophy of the gastric mucosa and carcinogenic risk. *Digestion.* 2015;91:30–6.
108. Fassan M, Pizzi M, Farinati F, Nitti D, Zagonel V, Genta RM, et al. Lesions indefinite for intraepithelial neoplasia and OLGA staging for gastric atrophy. *Am J Clin Pathol.* 2012;137:727–32.
109. Gupta S, Li D, El Serag HB, Davitkov P, Altayar O, Sultan S, et al. AGA Clinical Practice Guidelines on management of gastric intestinal metaplasia. *Gastroenterology.* 2019.
110. den Hollander WJ, Holster IL, den Hoed CM, Capelle LG, Tang TJ, Anten M-P, et al. Surveillance of premalignant gastric lesions: a multicentre prospective cohort study from low incidence regions. *Gut.* 2019;68:585–93.
111. Tsai Y-C, Hsiao W-H, Yang H-B, Cheng H-C, Chang W-L, Lu C-C, et al. The corpus-predominant gastritis index may serve as an early marker of *Helicobacter pylori*-infected patients at risk of gastric cancer. *Aliment Pharmacol Ther.* 2013;37:969–78.
112. Zhou Y, Li H-Y, Zhang J-J, Chen X-Y, Ge Z-Z, Li X-B. Operative link on gastritis assessment stage is an appropriate predictor of early gastric cancer. *World J Gastroenterol.* 2016;22:3670–8.
113. Cho S-J, Choi IJ, Kook M-C, Nam B-H, Kim CG, Lee JY, et al. Staging of intestinal- and diffuse-type gastric cancers with the OLGA and OLGIM staging systems. *Aliment Pharmacol Ther.* 2013;38:1292–302.
114. Altayar O, Davitkov P, Shah SC, Gawron AJ, Morgan D, Turner K, et al. AGA technical review on gastric intestinal metaplasia - epidemiology and risk factors. *Gastroenterology.* 2019.
115. Whiting JL, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JWL. The long term results of endoscopic surveillance of premalignant gastric lesions. *Gut.* 2002;50:378–81.
116. Zhang L, Liu Y, You P, Feng G. Occurrence of gastric cancer in patients with atrophic gastritis during long-term follow-up. *Scand J Gastroenterol.* 2018;53:843–8.
117. Li D, Bautista MC, Jiang S-F, Daryani P, Brackett M, Armstrong MA, et al. Risks and predictors of gastric adenocarcinoma in patients with gastric intestinal metaplasia and dysplasia: a population-based study. *Am J Gastroenterol.* 2016;111:1104–13.
118. Lim H, Jung H-Y, Park YS, Na HK, Ahn JY, Choi JY, et al. Discrepancy between endoscopic forceps biopsy and endoscopic resection in gastric epithelial neoplasia. *Surg Endosc.* 2014;28:1256–62.
119. Pimentel-Nunes P, Mourão F, Veloso N, Afonso LP, Jácome M, Moreira-Dias L, et al. Long-term follow-up after endoscopic resection of gastric superficial neoplastic lesions in Portugal. *Endoscopy.* 2014;46:933–40.
120. Zhao G, Xue M, Hu Y, Lai S, Chen S, Wang L. how commonly is the diagnosis of gastric low grade dysplasia upgraded following endoscopic resection? A meta-analysis. *PLoS One.* 2015;10:e0132699.
121. Noh C-K, Jung MW, Shin SJ, Ahn JY, Cho HJ, Yang MJ, et al. Analysis of endoscopic features for histologic discrepancies between biopsy and endoscopic submucosal dissection in gastric neoplasms: 10-year results. *Dig Liver Dis.* 2019;51:79–85.

122. Yang L, Jin P, Wang X, Zhang T, H.e YQ, Zhao XJ, et al. Risk factors associated with histological upgrade of gastric low-grade dysplasia on pretreatment biopsy. *J Dig Dis.* 2018;19:596–604.
123. Lauwers GY, Riddell RH. Gastric epithelial dysplasia. *Gut.* 1999;45:784–90.
124. Nam HS, Kim HW, Choi CW, Kang DH, Park SB, Kim SJ, et al. Characteristics of overlooked synchronous gastric epithelial neoplasia after endoscopic submucosal dissection. *Medicine (Baltimore).* 2018;97:e12536.
125. Lee T-Y, Wang R-C, Lee T-Y, Lin J-T, H.o HJ, Hsieh M-C, et al. The incidence of gastric adenocarcinoma among patients with gastric intestinal metaplasia: a long-term cohort study. *J Clin Gastroenterol.* 2016;50:532–7.
126. Yamada H, Ikegami M, Shimoda T, Takagi N, Maruyama M. Long-term follow-up study of gastric adenoma/dysplasia. *Endoscopy.* 2004;36:390–6.
127. Kato M, Nishida T, Tsutsui S, Komori M, Michida T, Yamamoto K, et al. Endoscopic submucosal dissection as a treatment for gastric noninvasive neoplasia: a multicenter study by Osaka University ESD Study Group. *J Gastroenterol.* 2011;46:325–31.
128. Choi CW, Kang DH, Kim HW, Park SB, Kim S, Cho M. Endoscopic submucosal dissection as a treatment for gastric adenomatous polyps: predictive factors for early gastric cancer. *Scand J Gastroenterol.* 2012;47:1218–25.
129. Ryu DG, Choi CW, Kang DH, Kim HW, Park SB, Kim SJ, et al. Clinical outcomes of endoscopic submucosa dissection for high-grade dysplasia from endoscopic forceps biopsy. *Gastric Cancer.* 2017;20:671–8.
130. Abe S, Oda I, Minagawa T, Sekiguchi M, Nonaka S, Suzuki H, et al. Metachronous gastric cancer following curative endoscopic resection of early gastric cancer. *Clin. Endosc.* 2018;51:253–9.
131. Yoon SB, Park JM, Lim C-H, Kim JS, Cho YK, Lee B-I, et al. Incidence of gastric cancer after endoscopic resection of gastric adenoma. *Gastrointest Endosc.* 2016;83:1176–83.
132. Cho CJ, Ahn JY, Jung H-Y, Jung K, O.h HY, N.a HK, et al. The incidence and locational predilection of metachronous tumors after endoscopic resection of high-grade dysplasia and early gastric cancer. *Surg Endosc.* 2017;31:389–97.
133. Moon HS, Yun GY, Kim JS, Eun HS, Kang SH, Sung JK, et al. Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: retrospective, single-center study. *World J Gastroenterol.* 2017;23:4407–15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28706423>
134. Chung GE, Chung SJ, Yang JI, Jin EH, Park MJ, Kim SG, et al. Development of metachronous tumors after endoscopic resection for gastric neoplasm according to the baseline tumor grade at a health checkup center. *Korean J Gastroenterol.* 2017;70:223–31.
135. Simone A, Casadei A, De Vergori E, Morgagni P, Saragoni L, Ricci E, et al. Rescue endoscopy to identify site of gastric dysplasia or carcinoma found at random biopsies. *Dig. Liver Dis.* 2011;43:721–5.
136. Yep-Gamarra V, Díaz-Vélez C, Araujo I, Ginès À, Fernández-Esparrach G. [Usefulness of systematic chromoendoscopy with a double dye staining technique for the detection of dysplasia in patients with premalignant gastric lesions]. *Gastroenterol Hepatol.* 2016;39:49–54.
137. Kim J-W, Jang JY. Optimal management of biopsy-proven low-grade gastric dysplasia. *World J Gastrointest Endosc.* 2015;7:396–402.