Gastritis: The histology report

Massimo Rugge [a,b,*], Gianmaria Pennelli [a], Emanuela Pilozzi [c], Matteo Fassan [a],
Giuseppe Ingravallo [d], Valentina M. Russo [e], Francesco Di Mario [f]

On behalf of the "Gruppo Italiano Patologi Apparato Digerente (GIPAD)" and of the "Società Italiana
di Anatomia Patologica e Citopatologia Diagnostica"/International Academy of Pathology,
Italian division (SIAPEC/IAP)

[a]*Department of Medical Diagnostic Sciences & Special Therapies (Surgical Pathology & Cytopathology Section), University of Padova, Padova, Italy*
[b]*Istituto Oncologico del Veneto IOV-IRCCS, Padova, Italy*
[c]*Department of Pathology, University of Roma La Sapienza, Roma, Italy*
[d]*Department of Pathological Anatomy, University of Bari, Bari, Italy*
[e]*Department of Pathological Anatomy, Garibaldi Hospital Catania, Italy*
[f]*Department of Gastroenterology, University of Parma, Parma, Italy*

Abstract

Gastritis is defined as inflammation of the gastric mucosa. In histological terms, it is distinguishable into two main categories, i.e. non-atrophic and atrophic. In the gastric mucosa, atrophy is defined as the loss of appropriate glands. There are several etiological types of gastritis, their different etiology being related to different clinical manifestations and pathological features. Atrophic gastritis (resulting mainly from long-standing *Helicobacter pylori* infection) is a major risk factor for the onset of (intestinal type) gastric cancer. The extent and site of the atrophic changes correlate significantly with the cancer risk. The current format for histology reporting in cases of gastritis fails to establish an immediate link between gastritis phenotype and risk of malignancy. Building on current knowledge of the biology of gastritis, an international group of pathologists [Operative Link for Gastritis Assessment (OLGA)] has proposed a system for reporting gastritis in terms of its stage (the OLGA Staging System): this system places the histological phenotypes of gastritis on a scale of progressively increasing gastric cancer risk, from the lowest (Stage 0) to the highest (Stage IV). The aim of this tutorial is to provide unequivocal information on how to standardize histology reports on gastritis in diagnostic practice.
© 2011 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

Keywords: Atrophic gastritis; Gastritis; GIPAD report; *Helicobacter pylori*; OLGA staging

1. Introduction

Gastritis defines any (histologically confirmed) inflammation of the gastric mucosa. Worldwide, the epidemiology of gastritis overlaps that of *Helicobacter pylori* (*H. pylori*) infection, which affects approximately 50% of the world's population. More definite epidemiological information is unavailable, but the incidence of gastritis around the world consistently parallels people's socio-economic status.

Assessing gastritis involves a clinical examination, serology (pepsinogens and antibodies against infectious agents and/or auto-antigens), endoscopy (applying standardized biopsy protocols), and histology to distinguish between non-atrophic and atrophic gastritis [1–5].

There is a large body of information to indicate that gastric atrophy is the primary risk factor for the onset of intestinal-type (or so-called "epidemic") gastric cancer (GC) [6–12]. Atrophy of the gastric mucosa (with and without

* Correspondence to: Massimo Rugge, MD, FACG, Chair of the Surgical Pathology and Cytopathology Unit, Università degli Studi di Padova, Istituto Oncologico del Veneto IOV-IRCCS, Via Aristide Gabelli, 61, 35121 Padova, Italia.

E-mail address: massimo.rugge@unipd.it (M. Rugge).

intestinal metaplasia) is considered the "field cancerization" for the development of gastric cancer. Intestinalized glands are prone to neoplastic transformation (i.e. non-invasive or intraepithelial neoplasia; acronyms: NiN and IEN), which have the potential for evolving into invasive adenocarcinoma [13–17]. There is some evidence of intestinal metaplasia also being reversible (after eradicating *H. pylori* infection and/or using chemoprevention strategies), while the chances of halting the progression of NiN to cancer are considerably lower; high-grade NiN virtually always evolves into (or coexists with) invasive adenocarcinoma [4,11].

In spite of the greater consistency achieved thanks to the Sydney System and its updated 1996 Houston version, the commonly-used nomenclature for gastritis remains inconsistent. Non-standard histology reporting formats are still widely used for gastritis and even specialists are often frustrated by histological definitions that make it difficult to identify candidates for clinico/endoscopic surveillance [8,10,18–24].

Building on current knowledge of the natural history of gastritis and the associated cancer risk, an international group of gastroenterologists and pathologists (the Operative Link for Gastritis Assessment [OLGA]) has proposed a system for reporting gastritis in terms of stage (the OLGA Staging System), which arranges the histological phenotypes of gastritis along a scale of progressively increasing gastric cancer risk, from the lowest (OLGA stage 0) to the highest (OLGA stage IV) [25–31]. This staging framework is borrowed from the oncology vocabulary and it applies to gastritis a histology reporting format successfully adopted for chronic hepatitis [32,33]. Just as a given number of portal tracts is required for the accurate staging of hepatitis, a well-defined biopsy sampling protocol (as recommended by the Sydney System) is a "minimum requirement" for the reliable staging of gastritis [21,34–36].

Gastritis is staged by combining the extent of atrophy (scored histologically) with its topographical location (resulting from the mapping protocol) [27,37]. In line with the Sydney recommendations, the OLGA staging system also includes information on the likely etiology of the gastric inflammatory disease (e.g. *H. pylori*, autoimmune, etc.).

The purpose of this tutorial is to provide a consistent frame for routine histology reporting on cases of gastritis. Basic lesions included in the histological spectrum of gastritis are only briefly addressed. Based on etiological considerations, the most common histological phenotypes of gastric inflammation are discussed. Moreover, given the clinical impact of the distinction between atrophic and non-atrophic gastritis, the OLGA staging system is described in detail to offer practical guidance on how to approach the basic histology report.

2. Gastritis: basic morphology [18,21]

2.1. Inflammatory infiltrate: mononuclear cells

Inflammatory infiltrate consists mainly of lymphocytes (dispersed or organized in follicular/nodular structures), plasma cells, histiocytes, and granulocytes within the lamina propria (and sometimes within the single glands units).

The term "lymphocytic gastritis" is used when lymphocytes are detected within the glandular epithelia; it is suggestive (but not diagnostic) of an immunomediated component of the inflammatory disease [18]. A more severe (nodular) intra-glandular lymphocytic infiltrate destroys and/or partially replaces the continuity of the glandular structure: such "lympho-epithelial lesions" are almost pathognomonic of primary gastric lymphomas (almost always associated with *H. pylori*).

2.2. Inflammatory infiltrate: polymorphs (neutrophils and eosinophils)

"Active" inflammation in the gastric mucosa is defined by the presence of neutrophils (within the lamina propria and/or the glandular lumen). A case where the eosinophils are predominant is described as "eosinophilic gastritis". The etiopathogenesis and clinical impact of such a histological category is still not clear.

2.3. Fibrosis of the lamina propria and smooth muscle hyperplasia

Expansion of the collagen tissue of the lamina propria (fibrosis) is associated with the loss of glandular units and the lesion is defined as mucosal atrophy. Fibrosis of the lamina propria may also be focal (i.e. scarring after peptic ulcer). Hyperplasia of the *muscularis mucosae* may result from long-term PPI therapy. Smooth muscle fascicles may push the glandular coils apart, giving rise to a pseudo-atrophic pattern.

2.4. Hyperplasia of the columnar epithelia

All inflammatory conditions of the gastric mucosa are associated with some degree of regenerative epithelial changes (regenerative hyperplasia) and this is typically seen at sites associated with erosions and peptic ulcers. Expansion of the proliferative compartment of the gastric glands (in the neck region) leads to foveolar hyperplasia. Chemicals (NSAID, biliary reflux into the stomach) or infectious stimuli that increase the cell turnover result in hyperplastic *foveolae*. An atypical regeneration of the glandular neck and/or expansion of the glandular proliferative compartment may make it difficult to differentiate regenerative from dysplastic lesions (the so-called "indefinite for non-invasive neoplasia" lesions). Changes occurring in the oxyntic epithelia as a result of treatment with proton pump inhibitors, in response to the acid secretion being inhibited, are sometimes considered as hyperplastic changes, but they may simply represent a remodeling of the epithelial structure due to cytoskeletal rearrangements.

2.5. Gastric mucosa atrophy

Normal gastric biopsy samples feature different populations of glands (mucosecreting or oxyntic), appropriate for the functional compartment (antrum or corpus) from which the specimen is obtained (i.e. "appropriate glands") [38–40] (Fig. 1). Occasionally, minuscule foci of metaplastic (goblet) cells may be encountered in the foveolar epithelium (i.e. "foveolar-restricted intestinal metaplasia"), but the overall density of appropriate glands is not affected.

The current definition of gastric atrophy is "loss of appropriate glands". In accordance with this definition, an international group of gastrointestinal pathologists arranged the histological spectrum of atrophic changes into a formal classification (Table 1).

Different phenotypes of atrophic transformation may be encountered, i.e.

(1) Shrinkage or complete disappearance of glandular units, replaced by expanded (fibrotic) lamina propria. Such a situation results in a reduced glandular mass, but does not imply any modification of the original cell phenotype (Fig. 1). Sometimes (particularly in *H. pylori*-associated gastritis), severe inflammation obscures the gland's population, making a reliable assessment of mucosal atrophy impossible. Such cases can be (temporarily) labeled as "indefinite for atrophy" and the final judgment can be deferred until the inflammation has regressed (e.g. after eradication of the *H. pylori* infection);

(2) Replacement of the native glands by metaplastic glands featuring a new commitment (= intestinal and/or pseudo-pyloric metaplasia). The number of glands is not necessarily lower, but the metaplastic replacement of native glands results in fewer glandular structures being "appropriate" for the compartment concerned. Such a condition is consistent with the definition of "loss of appropriate glands" (Fig. 1).
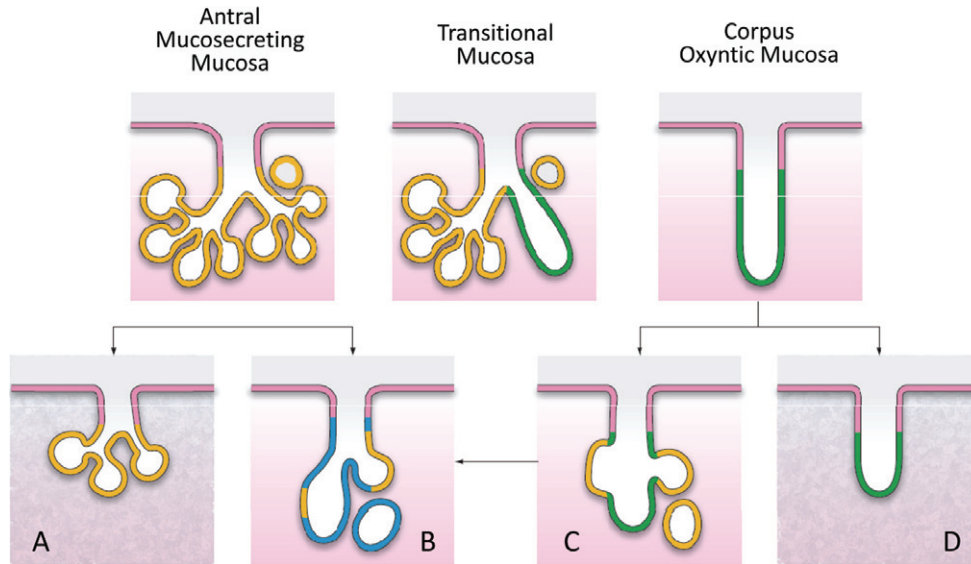

Fig. 1. Normal and atrophic glandular units in the stomach. Different types of gastric native mucosa are shown in the top (yellow line indicates mucosecreting antral glands; green line indicates oxyntic glands; in between, the transitional mucosa shows both oxyntic and mucosecreting commitment). Atrophic changes occuring in the different types of gastric mucosa are also shown: (A) Shrinkage of an antral glandular unit coexisting with fibrotic lamina propria; (B) Intestinal metaplasia of antral (mucosecreting) gland (blue line indicates IM); (C) Metaplastic "antralization" of oxyntic gland (pseudopyloric metaplasia = yellow line); (D) Shrinkage of an oxyntic glandular unit, partially replaced by fibrotic lamina propria. Pseudopyloric metaplastic glands may further undergo intestinalization (C → B).

Table 1
Atrophy in the gastric mucosa: histological classification and grading

ATROPHY				
0. Absent (= score 0)				
1. Indefinite (no score is applicable)				
2. Present	Histological type	Location & key lesions		Grading
		Antrum	Corpus	
	2.1. Non-metaplastic	Gland disappearance (shrinking) Fibrosis of the lamina propria		2.1.1. Mild = G1 (1–30%) 2.1.2. Moderate = G2 (31–60%) 2.1.3. Severe = G3 (>60%)
	2.2. Metaplastic	Metaplasia: – Intestinal	Metaplasia: – Pseudo-pyloric – Intestinal	2.2.1. Mild = G1 (1–30%) 2.2.2. Moderate = G2 (31–60%) 2.2.3 Severe = G3 (>60%)

Metaplasia is a transformation of the native commitment of a cell (never associated with "dedifferentiation") and any metaplastic transformation of the gastric glands implies loss of the appropriate glandular population (and therefore atrophy). There are two main types of gastric gland metaplasia. Pseudo-pyloric metaplasia (or spasmolytic polypeptide-expressing metaplasia [SPEM]) of the oxyntic epithelia is characterized by antral-like mucosa obtained from what was anatomically corpus mucosa [41–43]. It is particularly important for the endoscopist to identify the location of the biopsy specimens otherwise the pathologist is likely to miss the fact that this antral-like mucosa is metaplastic. The original oxyntic commitment of a pseudo-pyloric epithelium can be revealed by immunostaining for pepsinogen I (which is only found in oxyntic mucosa).

Intestinal metaplasia (IM) may arise in native mucosecreting (antral) epithelia or in previously-antralized oxyntic glands (pseudo-pyloric metaplasia). Different subtypes of intestinal metaplasia have been classified, based on whether the metaplastic epithelium phenotype resembles large bowel epithelia (colonic-type intestinal metaplasia) or the small intestinal mucosa [17,18]. In routine histology, subtyping IM by applying specific histochemical stains (high-iron diamine [HID]) is not recommended. Consistent data are available to demonstrate that the extent of gastric mucosa intestinalization parallels the histochemical demonstration of type II–III IM (colonic-type metaplasia).

2.6. Endocrine (enterochromaffin-like) cell hyperplasia

Endocrine cell hyperplasia is most frequently secondary to gastric hypo/achlorhydria as a result of oxyntic atrophy. Hyperplasia of the endocrine enterochromaffin-like cells (ECL) may be micronodular or diffuse. Less frequently, (neuro)endocrine (nodular) tumors (well-differentiated endocrine tumors; i.e. Type I carcinoids) may develop. It is important to mention that such tumors often regress after the source of gastrin has been removed (i.e. by antral resection) and they almost never metastasize (these lesions have been extensively addressed in this issue of *Digestive and Liver Disease* by Rindi et al. [44]).

2.7. Non-invasive neoplasia (formerly dysplasia; synonym: intraepithelial neoplasia)

In long-standing (atrophic) gastritis, mainly due to *H. pylori* infection, the metaplastic (intestinalized) epithelia are prone to further transformation, which may result in a dedifferentiated epithelium. This particular phenotype was once defined as dysplasia. Dysplastic epithelia are confined within the basal membrane of the native glandular structure. In dysplastic epithelia, molecular studies have consistently demonstrated a number of genotypic alterations similar to those detectable in cancer cells. The biological similarity between dysplasia and cancer has led to dysplasia being renamed as non-invasive (or intraepithelial) neoplasia (i.e. neoplasia confined by a continuous basal membrane) [19,20].

The continuity/integrity of the basal membrane separates the neoplastic epithelia from the stroma (i.e. *lamina propria*). This topographical separation rules out the stromal invasion required for any metastatic spread.

3. Gastritis classification [5]

Current classifications of gastritis are based on etiology. Table 2 summarizes the classification of gastritis etiologies, also illustrating their most frequent clinical presentations and their non-atrophic or atrophic phenotype.

4. Main forms of gastritis [18,21,39]

4.1. Helicobacter pylori gastritis

H. pylori is by far the most common etiological agent in gastritis. At histology, the bacterium is usually detectable (by Giemsa staining modified for *H. pylori*) within the mucous gel layer covering the gastric mucosa. *H. pylori* may be difficult to detect (even with special stains) in cases of extensive intestinal metaplasia, or during antisecretory (PPI) therapy; in such cases, the *H. pylori* infection is suggested by the presence of both mononuclear and neutrophilic ("active") inflammation. After successful eradication therapy, the neutrophils quickly disappear and any persistence of neutrophils and/or mononuclear infiltrate are an indication of the failure of the treatment. In routine diagnostic practice, any semi-quantitative score of the bacterium's density has no clinically significant implications and a distinction between *H. pylori* negative versus positive status is considered adequate.

H. pylori infection is a major cause of gastric atrophy. Atrophic changes (both metaplastic and non-metaplastic) detected in a biopsy sample obtained from both the angularis incisura and the antral mucosa should first be seen as evidence of a *H. pylori* gastritis. In long-standing infection (i.e. in elderly people) or in young patients with the infection and concomitant risk factors, atrophic changes also typically occur in the oxyntic mucosa as pseudo-pyloric metaplasia, often coexisting with multifocal intestinal metaplasia (in the antrum and corpus). Such patients are at greater risk of gastric cancer [21].

4.2. Chemical gastritis/gastropathies

Duodenal (bile) reflux into the stomach (due to partial gastrectomy or dysmotility), aspirin (or other nonsteroidal anti-inflammatory drugs), and other chemical injuries (possibly alcohol, etc.) may result in a broad spectrum of histological mucosal lesions, associated with low-grade inflammation of the gastric mucosa. Given the mild nature of the inflammatory trait, these conditions are currently defined as chemical gastritis or gastropathies.

Exposure of the gastric mucosa to a noxious chemical environment accelerates the turnover of the gastric epithelium, consistently resulting in foveolar hyperplasia. A concomitant

Table 2
Etiological classification of gastritis

Etiological category	Agents	Specific etiology	Clinical presentation	Notes[†]
Transmissible agents	Virus	Cytomegalovirus	Acute	Non-atrophic**
		Herpes virus	Acute	Non-atrophic **
	Bacteria	*Helicobacter pylori*	Acute or chronic	Non-atrophic & atrophic, type B***
		Mycobacterium tuberculosis	? Acute	Non-atrophic*
		Mycobacterium avium complex	? Acute	Non-atrophic*
		Mycobacterium diphtheriae	Acute	Non-atrophic*
		Actinomyces	Acute	Non-atrophic*
		Spirochetes	Acute	Non-atrophic *
	Fungi	Candida	Acute	Non-atrophic**
		Histoplasma	Acute	Non-atrophic*
		Phycomycosis	Acute	Non-atrophic*
	Parasites	Cryptosporidium	Acute	Non-atrophic*
		Strongyloides	Acute	Non-atrophic*
		Anisakiasis	Acute	Non-atrophic*
		Ascaris lumbricoides	Acute	Non-atrophic*
Chemical agents (most frequently gastropathies)	Environment (dietary & drug-related)	Dietary factors	Chronic	Non-atrophic & atrophic***
		Drugs: NSAIDs, ticlopidine	Acute	Non-atrophic; type C***
		Alcohol	Acute	Non-atrophic; type C**
		Cocaine	Acute	Non-atrophic; type C*
		Bile (reflux)	Acute or chronic chronic chronic	Non-atrophic; type C***
Physical agents	Radiation		Acute or chronic	Non-atrophic and atrophic*
Immuno-mediated	Different pathogenesis	Autoimmune	Chronic	Atrophic (corpus); type A**
		Drugs (ticlopidine)	Acute	
		? Gluten	Chronic	Lymphocytic gastritis**
		Food sensitivity	Acute or chronic	Eosinophilic gastritis**
		H. pylori (autoimmune component)	Chronic	Non-atrophic & atrophic
		GVHD	Acute or chronic	Non-atrophic & atrophic*
		Idiopathic	Acute or chronic	
Idiopathic		Crohn's disease	? Chronic	Non-atrophic/focal atrophy**
		Sarcoidosis	? Chronic	Non-atrophic or focal atrophy*
		Wegener's granulomatosis	? Chronic	Non-atrophic or focal atrophy*
		Collagenous gastritis	Acute	Non-atrophic*

[†]Prevalence: ***high, **low, *very low.

histamine-mediated vascular response and the release of other pro-inflammatory cytokines produce vascular ectasia, edema, muscularis mucosa hyperplasia and variable mucosal fibrosis. Most chemical gastropathies are asymptomatic, but multiple (endoscopically detectable) erosions or ulcers may develop in some cases, even with bleeding. Atrophic changes are rare and histology usually features a puzzle of low-grade lesions such as inter-foveolar edema, foveolar hyperplasia, muscularis mucosa hyperplasia, and vascular ectasia.

4.3. Autoimmune gastritis

Autoimmune gastritis is typically restricted to the corpus (autoimmune aggression targeted on parietal cells associated with anti-parietal cell and anti-intrinsic factor antibodies). The full-blown clinical syndrome includes hypo/achlorhydria, hypergastrinemia, a low pepsinogen I/pepsinogen II ratio (which parallels the loss of the oxyntic gland population), and vitamin B12-deficient macrocytic anemia. Serum gastrin 17 levels frequently increase. The disease may coexist with other immuno-mediated diseases, such as Hashimoto's thyroiditis, insulin-dependent diabetes, and vitiligo.

In the early (non-atrophic) stage, the oxyntic mucosa shows a dense, full-thickness lymphocytic infiltrate. In a later (atrophic) stage, the oxyntic glands are replaced by metaplastic glandular units (pseudo-pyloric metaplasia at first, followed by the glands' intestinalization later on). Immunohistochemistry for pepsinogen I reveals the native nature of the pseudo-pyloric metaplastic glands (focally maintaining their "chimerical" ability to pepsinogen I secretion). Hypo/achlorhydria triggers gastrin hypersecretion (hyperplasia of gastrin-secreting cells in the antral mucosa with increased gastrin 17 levels), which stimulates the enterochromaffin-like (ECL) cells of the oxyntic compartment. Such a situation may result in ECL cell hyperplasia (both linear and micronodular); micronodular ECL cell hyperplasia may progress into well-differentiated endocrine tumor (type I carcinoid) [24,25]. Extensive gastric metaplastic atrophy is a risk factor for adenocarcinoma. *H. pylori* infection may coexist with autoimmune gastritis, and this condition is an additional factor for atrophic transformation and, as a consequence, for GC.

In clinical practice, the prevalence of the other gastritis etiologies is practically negligible. The majority of viral, bacterial and mycotic types of gastritis are associated with immunodeficiency and they are not significantly involved in the gastric oncogenetic pathway.

5. Gastritis staging: the OLGA system [27]

Gastritis can be assessed on two different levels. The basic level consists in recognizing and scoring the elementary lesions (mononuclear infiltrate, activity, glandular atrophy, etc.) assessed in a single biopsy. A higher level considers the topography, the extent and combination of the changes seen in single biopsy samples, and this assessment should be representative of the stomach disease as a whole.

Based on the assumption that a different extent and topographical distribution of atrophy expresses different clinico-biological situations (associated with a different cancer risk), the Houston-updated Sydney System established that multiple biopsy samples should be obtained to explore the different mucosa compartments [21]. Different biopsy locations have been recommended in the international literature for mapping the mucosa, all of them consistent with the general assumption that both the oxyntic and the antral mucosa have to be "explored", and that the incisura angularis is "highly informative" for the purpose of establishing the earliest onset of atrophic-metaplastic transformation [35]. The OLGA approach (basically consistent with the Houston-updated biopsy protocol [21]) recommends at least 5 biopsy samples from: 1) the greater and lesser curvatures of the distal antrum (A1–A2 = mucus-secreting mucosa); 2) the lesser curvature at the *incisura angularis* (A3), where the earliest atrophic-metaplastic changes tend to occur; and 3) the anterior and posterior walls of the proximal corpus (C1–C2 = oxyntic mucosa) (Fig. 2).

The information obtained enables patients to be placed somewhere along the path that leads chronic gastritis from the originally reversible inflammatory lesions (mainly limited to the antrum) to the atrophic changes extensively involving both functional compartments (antrum and corpus) and associated with a high risk of GC [34].

5.1. Biopsy sampling protocol, histology request form and biopsy handling

The approach to assessing gastritis is both clinical and histological: clinical features should always support the interpretation of the endoscopic and histological findings.
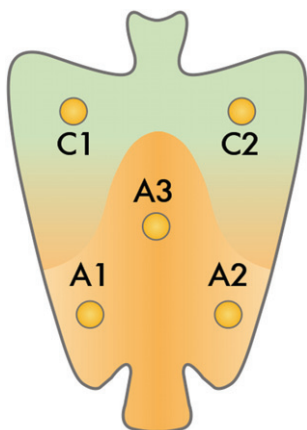

Fig. 2. Gastric biopsy sampling protocol.

Standardized biopsy protocols should be used, but many different biopsy sampling protocols have been proposed [4,8]. The most widely applied is the Sydney System protocol, in which mucosa from the oxyntic, antral, and *incisura angularis* areas are sampled (Fig. 1); the need to take additional specimens from any focal lesions has to be considered [9]. Antral and *incisura angularis* specimens can generally be placed in the same bottle, the corpus biopsies in another. If more extensive sampling of the corpus is done (e.g. 2 lesser curve and 2 greater curve specimens), then three bottles should be used (bottle 1= containing the 2 antral samples and the sample obtained from the *incisura angularis*; bottle 2: containing the 2 oxyntic samples from the anterior and posterior gastric wall; bottle 3: containing the samples obtained from the corpus mucosa samples obtained from the lesser and greater curvature).

Biopsy material should be handled as little as possible and, after fixation, it should be embedded on its edge. The basic stains to use are H&E and modified Giemsa (for *H. pylori*) [10,11].

Ideally, the histology request should be a dedicated form. It should include essential notes on the patient's clinical history and endoscopic features, and the biopsy sampling map. Non-invasive test findings (if any) should also be reported, e.g. pepsinogen levels, since pepsinogen (Pg) I occurs in fundic chief cells, while PgII is present in the antrum and corpus [13,14]. Gastrin 17 levels provide information on acid secretion (high gastrin serum levels = low acid secretion; low gastrin serum levels = typically means a high acid secretion). Testing for anti-parietal cell antibodies helps in the diagnosis of autoimmune gastritis.

The OLGA histology report also includes etiological information obtainable from the tissue samples available (i.e. *H. pylori* infection; autoimmune disease, etc.).

5.2. How to apply the OLGA staging system to gastritis

The OLGA system considers gastric atrophy as the lesion that indicates disease progression. The stage of gastritis is obtained by combining the extent of atrophy as scored histologically with the site(s) of atrophy identified by multiple biopsies (Fig. 3).

The following paragraphs are intended as a concise OLGA staging system "user's manual". Visual analog scales (VAS) are used to give an example of how the different changes seen at each of the biopsy sampling levels can be pieced together to stage a given patient (Figs. 4–9).

5.3. Scoring atrophy (loss of appropriate glands) at single biopsy level

In each biopsy, atrophy is scored as the percentage of atrophic glands. Ideally, atrophy is assessed on perpendicular (full-thickness) mucosal sections. Non-metaplastic and metaplastic subtypes are considered together. For each biopsy sample (whatever the area it comes from), atrophy is scored on a four-tiered scale (no atrophy, 0%, score = 0; mild

Atrophy Score		Corpus			
		No Atrophy (score 0)	Mild Atrophy (score 1)	Moderate Atrophy (score 2)	Severe Atrophy (score 3)
A n t r u m	No Atrophy (score 0) (including *incisura angularis*)	STAGE 0	STAGE I	STAGE II	STAGE II
	Mild Atrophy (score 1) (including *incisura angularis*)	STAGE I	STAGE I	STAGE II	STAGE III
	Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III	STAGE IV	STAGE IV

Fig. 3. The OLGA staging frame.

atrophy, 1–30%, score = 1; moderate atrophy, 31–60%, score = 2; severe atrophy, >60%, score = 3). These scores (0–3) are used in the OLGA staging assessment (Fig. 3).

5.4. Assessing atrophy in each compartment (mucosecreting and oxyntic)

According to the Sydney protocol, 3 biopsy samples should be taken from the mucosecreting area (2 antral samples + 1 from the *incisura angularis*), and 2 from the oxyntic mucosa. It is important to note that atrophic transformation in samples of incisura angularis mucosa is only assessed in terms of glandular shrinkage (with fibrosis of the lamina propria) or intestinal metaplasia (replacing original mucosecreting and/or oxyntic glands).

In each of the 2 mucosal compartments (mucosecreting and oxyntic), an overall atrophy score expresses the percentage of compartmental atrophic changes (pooling the findings in biopsies obtained from the same functional compartment). The same cut-offs are used at this higher assessment level as for single biopsies (no atrophy, 0%, score = 0; mild atrophy, 1–30%, score = 1; moderate atrophy, 31–60%, score = 2; severe atrophy, >60%, score = 3). Using this strategy, an overall atrophy score is obtained that separately summarizes the scores for the mucosa in the antrum ([Aas] Aas0, Aas1, Aas2, Aas3) and the corpus ([Cas] Cas0, Cas1, Cas2, Cas3) (Figs. 4–9).

The OLGA stage is obtained by combining the overall "antrum score" with the overall "corpus score" (Fig. 3).

6. From atrophy score to OLGA stage [27]

6.1. Stage 0 gastritis (i.e. non-atrophic mucosa) (Fig. 4)

When the overall score for atrophy is 0 in both the mucosecreting and the oxyntic compartments (meaning that none of the 5 standard biopsy samples reveals atrophy), the OLGA stage is obviously 0. The score for inflammatory lesions is independent of this staging, except in cases judged "indefinite for atrophy", in which case the florid inflammatory infiltrate may prevent the proper assessment of any loss of appropriate glands (eventually preventing the Stage assess-

ment). To avoid confounding the issue, all the VAS provided have been cleansed of any inflammatory component and no mention is made of any grading of the inflammatory lesions. The VAS refer to non-atrophic mucosa and are given as a standard reference to enable comparisons to be drawn with the "pathological" VAS.

6.2. Stage I gastritis (Fig. 5)

Stage I gastritis is the lowest "atrophic" stage. In most cases (especially in *H. pylori*-infected patients), atrophic lesions are only patchy and only found in some of the biopsy samples available. The atrophy is most frequently detected in angularis incisura samples. *H. pylori* status (as positive or negative) must be explicitly reported as an essential part of the OLGA format (while a semiquantitative assessment of *H. pylori* has little or no clinical impact). In patients on proton pump inhibitors [PPI], *H. pylori* may be difficult (or even impossible) to identify histologically at antral or corpus level, in which case coexisting inflammatory lesions (polymorphs and lymphoid infiltrate) may suggest the bacterium's presence and a comment on the suspected bacterial etiology ("suspicious for *H. pylori* infection") should be added (whatever the stage of atrophy recorded).

Together, Stage 0 and Stage I account for the vast majority of patients who undergo endoscopy for dyspepsia (with no alarming symptoms). Neither of these stages have ever been demonstrably associated with a greater risk of intestinal-type GC [3]. In cases of *H. pylori* infection, it is worth considering treatment to eradicate the bacterium.

6.3. Stage II gastritis (Fig. 6)

This may result from a combination of different (low-level) atrophy scores, which may concern the mucosecreting and/or oxyntic mucosa (notably, atrophy is detected in the distal mucosa biopsy samples in most cases). *H. pylori* status has to be reported (see above). From preliminary experience with OLGA staging, Stage II is frequently found in the low GC risk epidemiological setting [28]. Notably, Stages 0, I, and II are those in which duodenal ulcers are more frequent than gastric ulcers [30].
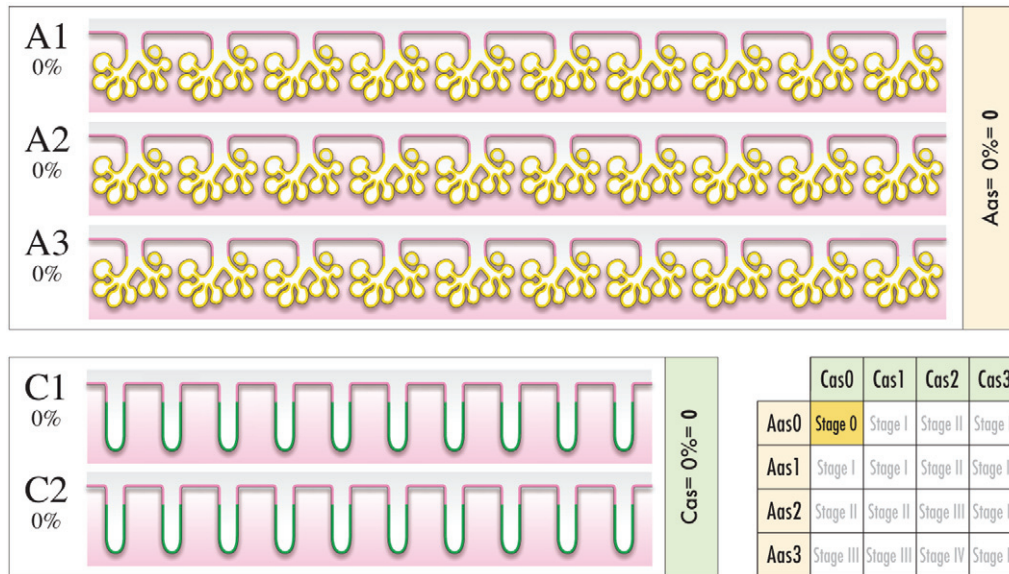
Fig. 4. Stage 0 gastritis. All 5 biopsy samples (3 from the mucosecreting compartment and 2 from the oxyntic compartment) consist of normal glands. This figure shows a normal gastric mucosa in both the antrum and the corpus. Each strip (= 1 biopsy sample) is labeled according to its site of origin (antral/angular = A; corpus = C) and includes 10 glandular units. Any inflammation (lymphocytes, monocytes, plasma cells, granulocytes) is disregarded. The percentages given on the left refer to the proportion of atrophic glands at single biopsy level (in this VAS, the percentage of atrophy is 0 in all available biopsies). The total ("compartmental") prevalence of atrophy is given on the right, distinguishing between antrum and corpus; the final "compartment atrophy score" is also shown. The OLGA staging frame is provided in the bottom right-hand corner, where the OLGA stage is reported (OLGA stage 0). *H. pylori*-status (as histologically assessed by special stain) has to be reported.
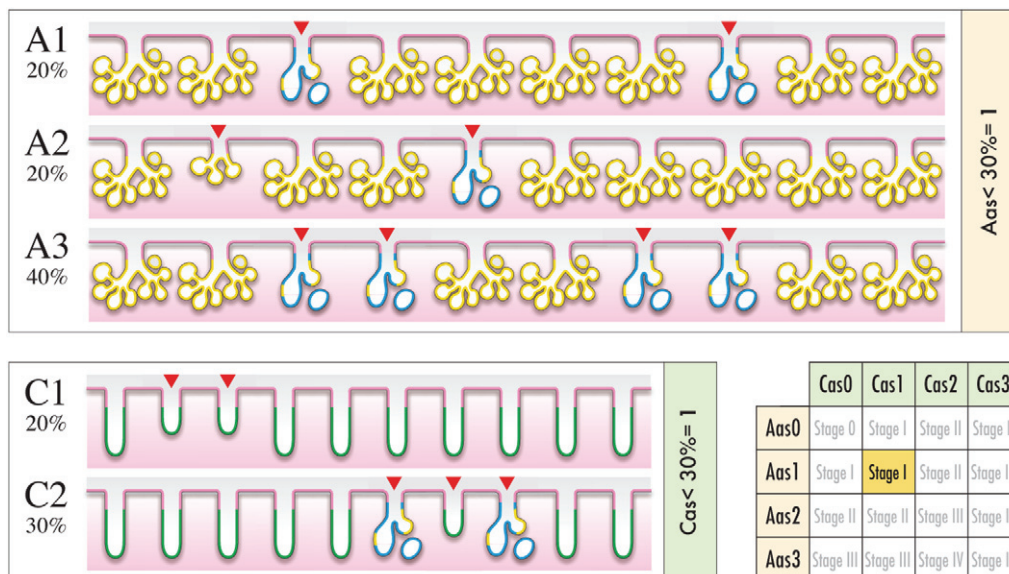

Fig. 5. Stage I gastritis. Scoring atrophy in each antral/angular biopsy (atrophic glands are identified by a red marker): A1 = 20%; A2 = 20%; A3 = 40%.
Assessing atrophy at compartment level (antrum): dividing 80 (= 20 + 20 + 40) by 3 (the number of antral biopsies considered), the final antral atrophy score (Aas) is 27% (<30%), which means a score of 1.
Scoring atrophy in each corpus biopsy (atrophic glands are identified by a red marker): C1 = 20%; C2 = 30%.
Assessing atrophy at compartment level (corpus): dividing 50 (= 20 + 30) by 2 (the number of corpus biopsies considered), the final corpus atrophy score (Cas) is 25% (<30%), which means a score of 1.
Combining the atrophy scores for the antrum (antral atrophy score [Aas] = 1) and corpus (corpus atrophy score [Cas] = 1) gives the OLGA stage, as shown in the reference chart (bottom right-hand corner: OLGA stage I). *H. pylori*-status (as histologically assessed by special stain) has to be reported.

6.4. Stage III gastritis (Figs. 7 and 8)

Stage III gastritis results from multifocal atrophy at mucosecreting and/or oxyntic level. The metaplastic variant of atrophy is consistently detectable. The phenotype of Stage III gastritis recalls that of the multifocal atrophic gastritis (MAG) described by Pelayo Correa: as in Correa's MAG, gastric peptic ulcer can be encountered more frequently than in OLGA stages 0–I–II [4,18,30]. *H. pylori* status has to be reported (see above). When Stage III is found in patients
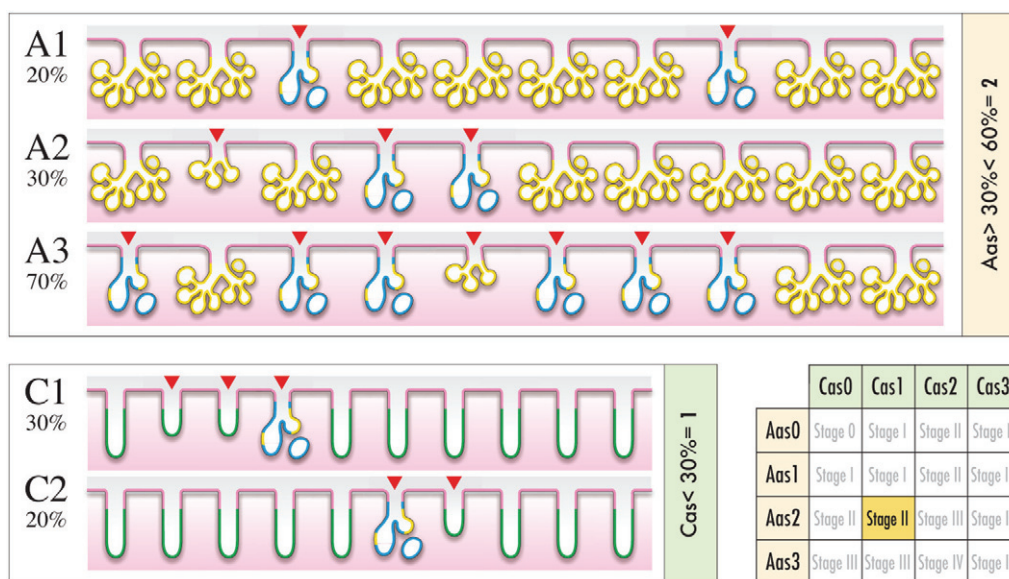
Fig. 6. Stage II gastritis. Scoring atrophy in each antral/angular biopsy (atrophic glands are identified by a red marker): A1 = 20%; A2 = 30%; A3 = 70%.
Assessing atrophy at compartment level (antrum): dividing 120 (= 20 + 30 + 70) by 3 (the number of biopsies considered), the final antral atrophy score (Aas) is 40% (>30% <60%), which means a score of 2.
Scoring atrophy in each corpus biopsy (atrophic glands are identified by a red marker): C1 = 30%; C2 = 20%.
Assessing atrophy at compartment level (corpus): dividing 50 (= 30 + 20) by 2 (the number of biopsies considered), the final corpus atrophy score (Cas) is 25% (<30%), which means a score of 1.
Combining the atrophy scores for the antrum (Aas = 2) and corpus (Cas = 1) gives the OLGA stage, as shown in the reference chart (bottom right-hand corner: OLGA stage II). *H. pylori*-status (as histologically assessed by special stain) has to be reported.
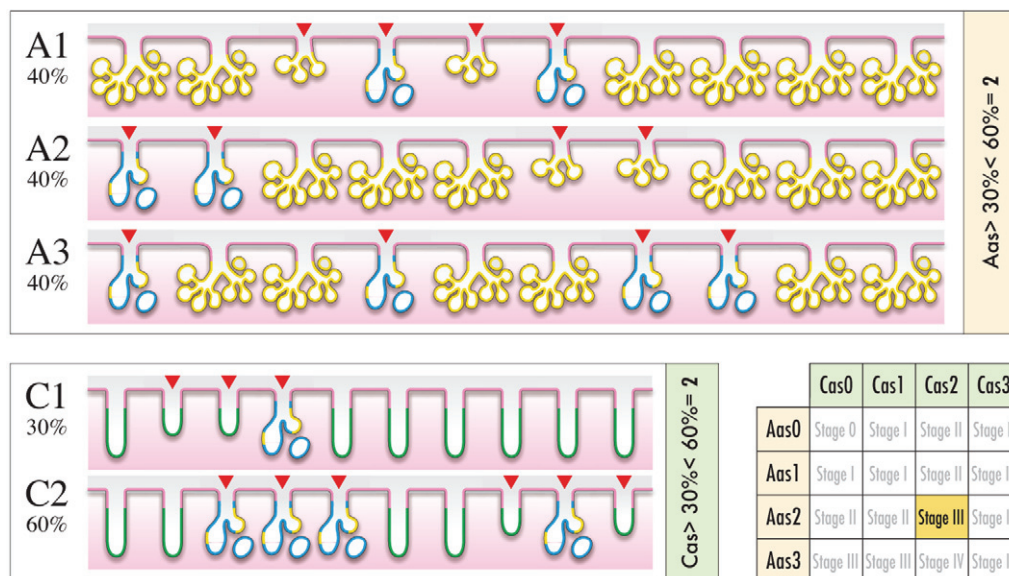

Fig. 7. Stage III gastritis. Scoring atrophy in each antral/angular biopsy (atrophic glands are identified by a red marker): A1 = 40%; A2 = 40%; A3 = 40%.
Assessing atrophy at compartment level (antrum): dividing 120 (= 40 + 40 + 40) by 3 (the number of biopsies considered), the final antral atrophy score (Aas) is 40% (>30% <60%), which means a score of 2.
Scoring atrophy in each corpus biopsy (atrophic glands are identified by a red marker): C1 = 30%; C2 = 60%.
Assessing atrophy at compartment level (corpus): dividing 90 (= 30 + 60) by 2 (the number of biopsies considered), the final corpus atrophy score (Cas) is 45% (>30% <60%), which means a score of 2.
Combining the atrophy scores for the antrum (Aas = 2) and corpus (Cas = 2) gives the OLGA stage, as shown in the reference chart (bottom right-hand corner: OLGA stage III). *H. pylori*-status (as histologically assessed by special stain) has to be reported.

with minimal antral atrophy, the etiological hypothesis of autoimmune atrophic gastritis needs to be considered. Stage III is rarely encountered in most populations at low risk of GC, and it may already coexist with intraepithelial or invasive neoplasia [40].

6.5. Stage IV gastritis (Fig. 9)

This means atrophy involving both antral and oxyntic mucosa, a situation basically corresponding to the pan-atrophic gastritis phenotype. In patients with *H. pylori* infection,
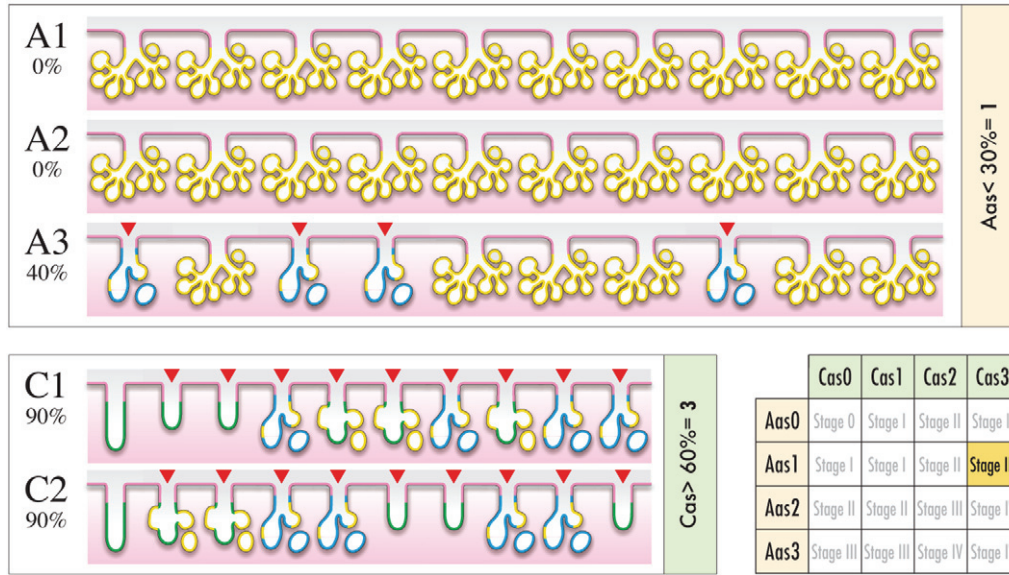
Fig. 8. Stage III gastritis. Scoring atrophy in each antral/angular biopsy (atrophic glands are always identified by a red marker): A1 = 0%; A2 = 0%; A3 = 40%. Assessing atrophy at compartment level (antrum): dividing 40 (= 0 + 0 + 40) by 3 (the number of biopsies considered), the final antral atrophy score (Aas) is 13% (<30%), which means a score of 1.
Scoring atrophy in each corpus biopsy (atrophic glands are identified by a red marker): C1 = 90%; C2 = 90%.
Assessing atrophy at compartment level (corpus): dividing 180 (= 90 + 90) by 2 (the number of biopsies considered), the final corpus atrophy score (Cas) is 90% (>60%), which means a score of 3.
Combining the atrophy scores for the antrum (Aas = 1) and corpus (Cas = 3) gives us the OLGA stage, as shown in the reference chart (bottom right-hand corner: OLGA stage III). *H. pylori* status (as histologically assessed by special stain) has to be reported. In this case, the pattern of atrophic gastritis (corpus predominant atrophy) should suggest an autoimmune etiology.
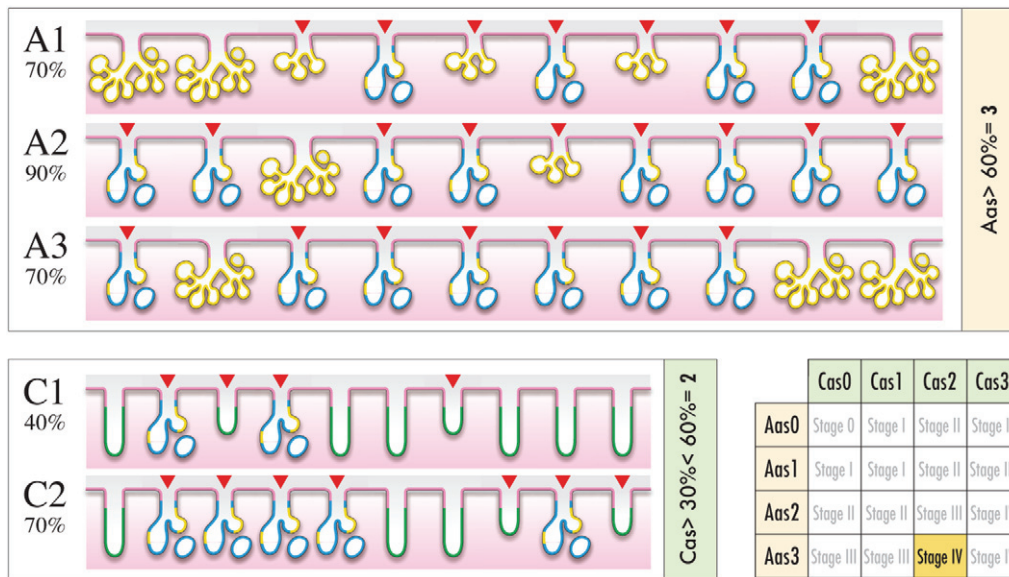

Fig. 9. Stage IV gastritis. Scoring atrophy in each antral/angular biopsy (atrophic glands are identified by a red marker): A1 = 70%; A2 = 90%; A3 = 70%. Assessing atrophy at compartment level (antrum): dividing 230 (= 70 + 90 + 70) by 3 (the number of biopsies considered), the final antral atrophy score (Aas) is 77% (>60%), which means a score of 3.
Scoring atrophy in each corpus biopsy (atrophic glands are identified by a red marker): C1 = 40%; C2 = 70%.
Assessing atrophy at compartment level (corpus): dividing 110 (= 40 + 70) by 2 (the number of biopsies considered), the final corpus atrophy score (Cas) is 55% (>30% <60%), which means a score of 2.
Combining the atrophy scores for the antrum (Aas = 3) and corpus (Cas = 2) gives the OLGA stage, as shown in the reference chart (bottom right-hand corner: OLGA stage IV). *H. pylori* status (as histologically assessed by special stain) has to be reported.

extensive metaplastic transformation can interfere with the bacterium's histological detection. This stage is rarely seen in areas with a low incidence of GC. Available data show a significantly higher risk of GC developing in (or being associated with) OLGA stage III–IV cases. Endoscopic surveillance programs should consequently concentrate on stage III–IV patients [28–30].

Table 3
The histology report: checklist

Section of histology report	Recommendations	Notes
Biopsy sample identification	– The biopsy samples should be identified (1,2, 3, etc., or A, B, C, etc.) as submitted (each vial). – Biopsy location (each vial) should be reported as submitted (quote the histology request form). – The number of biopsy samples delivered in the same vial should be reported.	Each biopsy sample should be explicitly associated with its gastric mucosa subsite (as identified during endoscopy procedure).
Clinical information	– The most pertinent clinical information should be reported (quote exactly from the histology request form).	When no clinical information is available, this should be noted (i.e. "no clinical information available").
Histology assessment (description and scoring of elementary lesions)	– Histology assessments should refer to each available specimen (as previously identified).	The main histology lesions should be scored according to the current literature (for lymphoid inflammation and activity, see Genta's visual analog scales; for atrophy scoring see the present text). Scoring *H. pylori* density is irrelevant.
Diagnostic statement	This includes OLGA stage and etiological hypothesis (*H. pylori*, autoimmune, chemical agents or combinations).	
Additional comments	If any (the finding of IEN has to be specifically noted and explicitly associated with its gastric mucosa subsite).	

7. How to prepare the histology report

The essential parts of the histology report are summarized in Table 3.

The material submitted (identified by numbers or letters) has to be listed according to the gastric sub-site from which each biopsy sample was obtained. The number of biopsy samples obtained from each site (and delivered in the same vial) has to be reported.

The available clinical information should be included in the histology report as provided in the histology request (the absence of clinical data should be mentioned). The clinical information mentioned in the histology report should include the indication for endoscopy, a brief description of endoscopic lesions (if any), previous *H. pylori* eradication therapy and/or other current therapies (NSAID, PPI, etc.).

The assessment/description of the elementary lesions (in each of the biopsy samples considered) represents the core element in the histology report. A semiquantitative score of some of the elementary lesions should be provided, i.e. (a) lymphoid-monocytic inflammation, (b) polymorphs (i.e. activity), (c) atrophy (distinguished as metaplastic and non-metaplastic), (d) *H. pylori* status (positive versus negative). Other histological lesions (i.e. foveolar hyperplasia, vascular ectasia) can simply be mentioned. Any advanced precancerous lesions (IEN) have to be reported specifically and explicitly associated with the biopsy sample(s) where they were identified.

According to the OLGA staging system, the final assessment should include the stage of gastritis and the etiological hypothesis, based on the overall gastritis phenotype.

8. Conclusions

Gastritis is assessed by obtaining histological proof of inflammatory cells within the gastric mucosa. Based on the definition of atrophy as the loss of appropriate glands, the recently proposed gastritis staging (OLGA) system may afford a reliable indication of the cancer risk of individual patients. Gastritis staging plainly expresses the cancer risk associated with atrophic gastritis and may help the physician to develop a clinical, serological or endoscopic management plan tailored to each patient's disease.

Conflict of interest

The authors have no conflict of interest to report.

References

[1] Pasechnikov VD, Chukov SZ, Kotelevets SM, et al. Invasive and non-invasive diagnosis of *Helicobacter pylori*-associated atrophic gastritis: a comparative study. Scand J Gastroenterol 2005;40(3):297–301.

[2] Rugge M. Secondary prevention of gastric cancer. Gut 2007;56(12):1646–7.

[3] Graham DY, Rugge M. Clinical practice: diagnosis and evaluation of dyspepsia. J Clin Gastroenterol 2010;44(3):167–72.

[4] Dore MP, Graham DY. Ulcers and gastritis 2009. Endoscopy;42(1):38–41.

[5] Lauwers GY, Fujita H, Nagata K, et al. Pathology of non-*Helicobacter pylori* gastritis: extending the histopathologic horizons. J Gastroenterol 2010;45(2):131–45.

[6] Filipe M, Munoz N, Matko I, et al. Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. Int J Cancer 1994;57(3):324–9.

[7] Sipponen P, Riihela M, Hyvärinen H, et al. Chronic nonatrophic

("superficial") gastritis increases the risk of gastric carcinoma. A case-control study. Scand J Gastroenterol 1994;29(4):336–40.

[8] Miehlke S, Hackelsberger A, Meining A, et al. Severe expression of corpus gastritis is characteristic in gastric cancer patients infected with *Helicobacter pylori*. Br J Cancer 1998;78(2):263–6.

[9] Cassaro M, Rugge M, Gutierrez O, et al. Topographic patterns of intestinal metaplasia and gastric cancer. Am J Gastroenterol 2000;95(6):1431–8.

[10] Uemura N, Okamoto S, Yamamoto S. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001;345(11):784–9.

[11] Rugge M, Cassaro M, Di Mario F, et al. Interdisciplinary Group on Gastric Epithelial Dysplasia (IGGED): The long-term outcome of gastric non-invasive neoplasia. Gut 2003;52(8):1111–6.

[12] Correa P. The biological model of gastric carcinogenesis. IARC Sci Publ 2004;157:301–10.

[13] Stemmermann G. Intestinal metaplasia of the stomach. A status report. Cancer 1994;74(2):556–64.

[14] Garcia S, Park HS, Novelli M, et al. Field cancerization, clonality, and epithelial stem cells: the spread of mutated clones in epithelial sheets. J Pathol 1999;187(1):61–81.

[15] Matsushima K, Isomoto H, Inoue N, , et al. MicroRNA signatures in *Helicobacter pylori*-infected gastric mucosa. Int J Cancer 2010. [Epub ahead of print]

[16] Vannella L, Lahner E, Osborn J, et al. Risk factors for progression to gastric neoplastic lesions in patients with atrophic gastritis. Aliment Pharmacol Ther 2010;31(9):1042–50.

[17] Niwa T, Tsukamoto T, Toyoda T, et al. Inflammatory processes triggered by *Helicobacter pylori* infection cause aberrant DNA methylation in gastric epithelial cells. Cancer Res 2010;70(4):1430–40.

[18] Correa P. Chronic gastritis: a clinico-pathological classification. Am J Gastroenterol 1988;83(5):504–9.

[19] Price AB. The Sydney System: histological division. J Gastroenterol Hepatol 1991;6(3):209–22.

[20] Whitehead R. The classification of chronic gastritis: current status. J Clin Gastroenterol 1995;21 Suppl 1:S131–4.

[21] Dixon M, Genta RM, Yardley JH, et al.Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20(10):1161–81.

[22] Genta RM. Recognizing atrophy: another step toward a classification of gastritis. Am J Surg Pathol 1996;20 Suppl 1:S23–30.

[23] Dixon M, Genta RM, Yardley JH, et al. Histological classification of gastritis and *Helicobacter pylori* infection: an agreement at last? The International Workshop on the Histopathology of Gastritis. Helicobacter 1997;2(Suppl 1):S17–24.

[24] Meining A, Riedl B, Stolte M. Features of gastritis predisposing to gastric adenoma and early gastric cancer. J Clin Pathol 2002;55(10):770–3.

[25] Rugge M, Genta RM. Staging gastritis: an international proposal. Gastroenterology 2005;129(5):1807–1808.

[26] Rugge M, Genta RM. Staging and grading of chronic gastritis. Hum Pathol 2005;36(3):228–33.

[27] Rugge M, Correa P, Di Mario F, et al. OLGA staging for gastritis: a tutorial. Dig Liver Dis 2008;40(8):650–8.

[28] Rugge M, Kim JG, Mahachai V, et al. OLGA gastritis staging in young adults and country-specific gastric cancer risk. Int J Surg Pathol 2008;16(2):150–4.

[29] Rugge M, de Boni M, Pennelli G, et al. OLGA can guard the barn. Am J Gastroenterol 2009;104(12):3099; author reply 3101–2.

[30] Rugge M, De Boni M, Pennelli G, et al. Gastritis OLGA-staging & gastric cancer risk: a twelve year clinico-pathological follow-up study. Aliment Pharmacol Ther 2010; 31(10):1104–11.

[31] Capelle LG, de Vries AC, Haringsma J, 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(7):1150–8.

[32] Desmet V, Gerber M, Hoofnagle JH, et al. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19(6):1513–20.

[33] UICC. TNM classification of malignant tumours. Seventh edition, 2009.

[34] Sipponen P, Stolte M. Clinical impact of routine biopsies of the gastric antrum and body. Endoscopy 1997;29(7):671–8.

[35] Rugge M, Cassaro M, Pennelli G, et al. Pathology and endoscopy in the reversibility assessment. Gut 2003;52(3):1387–8.

[36] Guido M, Rugge M. Liver biopsy sampling in chronic viral hepatitis. Semin Liver Dis 2004;24(1):89–97.

[37] Genta R. Gastritis on the stage. Adv Anat Pathol 2007;14(3):233.

[38] Ruiz B, Garay J, Correa P, et al. Morphometric evaluation of gastric antral atrophy: improvement after cure of *Helicobacter pylori* infection. Am J Gastroenterol 2001;96(12):3281–7.

[39] Rugge M, Correa P, Dixon MF, et al. Gastric mucosal atrophy: inter-observer consistency using new criteria for classification and grading. Aliment Pharmacol Ther 2002;16(7):1249–59.

[40] Rugge M, Meggio A, Pennelli G, et al. Gastritis staging in clinical practice: the OLGA staging system. Gut 2007;56(5):631–6.

[41] Gutiérrez-Gonzalez L, Wright NA. Biology of intestinal metaplasia in 2008: more than a simple phenotypic alteration. Dig Liver Dis 2008; 40(7):510–22.

[42] Weis VG, Goldenring JR. Current understanding of SPEM and its standing in the preneoplastic process. Gastric Cancer 2009;12(4):189–97.

[43] Nam KT, Lee HJ, Sousa JF, et al. Mature chief cells are cryptic progenitors for metaplasia in the stomach. Gastroenterology 2010; 139(6):2028–37.

[44] Rindi G, Bordi C, La Rosa S, et al. Gastroenteropancreatic (neuro) endocrine neoplasms: The histology report. Dig Liver Dis 2011;43 (Suppl 4):S356–60.