OLGA Gastritis Staging for the Prediction of Gastric Cancer Risk: A Long-term Follow-up Study of 7436 Patients

Massimo Rugge, MD, FACG[1,2], Robert M. Genta, MD[3,4], Matteo Fassan, MD, PhD[1], Elisa Valentini, MD[1], Irene Coati, MD[1], Stefano Guzzinati, MSc[2], Edoardo Savarino, MD[5], Manuel Zorzi, MD[2], Fabio Farinati, MD[5] and Peter Malfertheiner, MD[6]

OBJECTIVES: **Gastritis OLGA-staging ranks the risk for gastric cancer (GC) in progressive stages (0–IV). This long-term follow-up study quantifies the GC risk associated with each OLGA stage.**

METHODS: **Consecutive patients (7436) underwent esophagogastroscopy (T-0), with mapped gastric biopsies, OLGA staging, and *H. pylori* status assessment. Patients with neoplastic lesion (invasive or non-invasive) at the index endoscopy (and/or within 12 months) were excluded. All patients were followed-up (T-1) by combining different sources of clinical/pathological information (Regional Registries of: (i) esophagogastroduodenoscopies; (ii) pathology reports; (iii) cancer, (iv) mortality). The endpoint was histologically documented development of gastric epithelial neoplasia.**

RESULTS: **At T-0, the patients' distribution by OLGA stage was: Stage 0 = 80.8%; Stage I = 12.6%; Stage II = 4.3%; Stage III = 2.0%; Stage IV = 0.3%; *H. pylori* infection was detected in 25.9% of patients. At the end of the follow-up (mean/median = 6.3/6.6 years), 28 incident neoplasia were documented (overall prevalence = 0.60 per 10^3/person-years; low-grade intraepithelial neoplasia = 17/28; high-grade intraepithelial neoplasia = 4/28; GC = 7/28). By OLGA stage at the enrollment, the rate of incident neoplasia was: Stage 0 = 1 case; rate/10^3 person-years = 0.03; 95%CI: 0.004–0.19; Stage I = 2 cases; rate/10^3 person-years = 0.34; 95%CI: 0.09–1.36; Stage II = 3 cases; rate/10^3 person-years = 1.48; 95%CI: 0.48–4.58; Stage III = 17 cases; rate/10^3 person-years = 19.1; 95%CI: 11.9–30.7; Stage IV = 5 cases; rate/10^3 person-years = 41.2; 95%CI: 17.2–99.3. Multivariate analysis including gender, age, *H. pylori* status, and OLGA stage at enrollment only disclosed OLGA stage as predictor of neoplastic progression (OLGA stage III: HR = 712.4, 95%CI = 92.543–5484.5; OLGA stage IV: HR = 1450.7, 95%CI = 166.7–12626.0).**

CONCLUSIONS: **Among 7436 patients, OLGA stages at the enrollment correlated significantly with different risk for gastric neoplasia. Based on the obtained results, gastritis staging is a critical adjunct in endoscopy follow-up protocols aimed at GC secondary prevention.**

Am J Gastroenterol (2018) 113:1621–1628. https://doi.org/10.1038/s41395-018-0353-8

INTRODUCTION

Gastric cancer (GC) is one of five leading causes of death worldwide [1], with an overall 5-year survival rate ranging between 25 and 30% [2]. The crucial factor in such a frustrating prognosis is the advanced stage at which most gastric cancers are detected. Therefore, a viable strategy for curtailing deaths from gastric cancer should rely on the early detection and management of its precursor. Most gastric adenocarcinomas (typically the intestinal-type variant, most commonly arising in the distal stomach) are the ultimate step of a cascade of epithelial phenotypic changes, triggered by non-self-limiting inflammation [3–5].

Helicobacter pylori (*H. pylori*) infection is, by far, the most common etiologic agent of these inflammatory changes and, consequently, the most common cause of non-syndromic gastric cancer, often referred to as environmental cancer [6, 7]. The primary prevention of *H. pylori* infection and its timely eradication (before

[1]Department of Medicine (DIMED), Surgical pathology & Cytopathology Unit, University of Padova-Azienda Ospedaliera di Padova, Padova, Italy. [2]Veneto Tumor Registry, Veneto Region, Padova, Italy. [3]Departments of Pathology and Medicine, Baylor College of Medicine, Houston, TX, USA. [4]Inform Diagnostics Research Institute, Irving, TX, USA. [5]Department of Oncology and Gastroenterology (DISGOG), Gastroenterology Unit, University of Padova-Azienda Ospedaliera di Padova, Padova, Italy. [6]Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital, Magdeburg, Germany.
Correspondence: M.R. (email: massimo.rugge@unipd.it)
Received 22 February 2018; accepted 20 July 2018; Published online 17 October 2018

extensive atrophic changes develop) are currently considered as the most effective cancer preventing strategies. More than 95% of distal gastric adenocarcinomas arise in intestinalized glands, in a background of atrophic-metaplastic gastritis [8].

In a process of progressive de-differentiation, metaplastic cells may acquire most of the biological profile of neoplastic cells. When their native cohesive aptitude is preserved, the resulting change is referred as intraepithelial neoplasia (IEN), also known as dysplasia. In a further step, dysplastic cells may lose their cohesiveness and acquire the phenotype and the behavior of invasive cancer [9, 10]. Both extension and topographic distribution of gastric atrophy parallel the risk for GC, and several international guidelines suggest that patients with extensive atrophic gastritis be entered in endoscopic surveillance protocols [11–13].

Histological staging systems for gastritis rank the risk for gastric cancer in progressive stages, based on extension and topography of the atrophic-metaplastic changes, from 0 to IV. The Operative Link for Gastritis Assessment (OLGA) system has designated patients with stages III and IV as high-risk and has recommended dedicated follow-up [14–18]. The OLGIM (Operative Link for Gastric Intestinal Metaplasia) is based on a similar concept but considers only the extension and topography or intestinal metaplasia [19]. The prognostic value of both staging systems has now been documented in several studies involving cohorts of variable size [20–29].

This study was designed to quantify the GC risk associated with each different gastritis OLGA stage in a series of 7436 consecutive patients underwent had upper esophagogastroduodenoscopy (EGD) for the evaluation of dyspepsia [19, 30].

PATIENTS AND METHODS

Patients' selection (T-0)

This study included 7436 consecutive patients who underwent EGD between 2007 and 2011 at the Gastroenterology Unit of the University of Padua Hospital, a regional hospital located in Northeastern Italy. Indications for the endoscopy included dyspepsia, bloating, and epigastric pain and discomfort. The first EGD (index EGD) is designated as T-0. The study population was retrieved by searching the digital archives of the Department of Pathology. Among the registered cases, only patients who were residents of the regional area (Veneto) were considered (Fig. 1). After retrieving the records, the following inclusion criteria were applied: (i) age older than 18; (ii) no previous gastro-esophageal surgery; (iii) endoscopy procedure including at least 5 biopsy samples (2 from the antral mucosa; one from the *incisura angularis*; and 2 representative of the oxyntic mucosa); (iv) histological assessment of the gastritis stage according to the OLGA criteria (Table 1); (v) histological assessment of the *H. pylori* status as *H. pylori*-positive (*Hp*+ve) versus H. pylori-negative (*Hp*−ve); (vi) no previous or current clinico-pathological evidence of advanced gastric precancerous lesions (intraepithelial neoplasia) or neoplastic gastro-esophageal lesions. Cases in which gastric neoplastic lesions were detected within 12 months from the initial biopsy (T-0) were interpreted as prevalent neoplasia missed at the initial endoscopy and, therefore, were excluded.

Endoscopy procedures at T-0 and biopsy specimens' submission

All EGDs were performed or supervised by the same team of senior endoscopists (FF, ES) and were conducted either under oropharyngeal anesthesia or after sedation with midazolam or Propofol. As per clinical protocol, all patients were explicitly recommended to discontinue the use of Proton Pump Inhibitors (PPI) therapy at least 14 days before the scheduled endoscopy. Biopsy specimens were submitted to the Department of Pathology in two separate 10% formalin jars, one containing the samples from the corpus and one those from the antrum and the *incisura angularis* [31].

Helicobacter pylori status

H. pylori status was assessed by histology at T-0 using the Giemsa stain modified for *H. pylori*. Eradication therapy was recommended to all *H. pylori*-positive patients; however, no information was available on the outcome of the eradication (if any). *H. pylori* status at the end of the follow-up period is reported only for those patients in whom a neoplastic event occurred (histological assessment at T-1).

Histopathologic evaluation

All 7436 patients enrolled in this study underwent an initial (T-0) histological assessment based on five biopsy gastric mucosa samples (2 from the antrum, 2 f1 from the incisura angularis, and 32 from corpus mucosa); in all these patients the gastritis OLGA stage was assessed according to the OLGA 2008 guidelines [16, 31]. At the study center, the interobserver consistency in the assessment of the gastritis stage is calculated every year as part of the annual internal quality control evaluation. The *k*-statistics values in 2008 were: $k = 0.66$; 95%CI = 0.49–0.83; in 2011 they were: $k = 0.71$ 95%CI = 0.55–0.87. Both *k* values represent "substantial agreement."

Patients' follow-up (T-1) and vital status: sources and outcome measures

Information about any relevant clinical event that occurred in the entire study population after enrollment was obtained by consulting the following sources: (i) Regional registries of endoscopy procedures; (ii) Regional archives of histopathology reports; (iii) the Regional Cancer Registry; (iv) the Regional Mortality Registry.

Each patient accumulated person-time for follow-up analysis from the date of enrollment (T-0) to the date of gastric neoplasia incidence (histopathologic diagnosis of one of the considered neoplastic outcomes (i.e., LG-IEN, HG-IEN, invasive GC)), death, emigration, or last available follow-up, whichever came first (T-1). The vital status of all patients was assessed through record linkage with the population file of residents, as available from the Regional Healthcare System (RHS).

Cases of neoplastic lesions (both invasive and non-invasive) diagnosed from one the date of the initial endoscopy through January 2016 (end of the follow-up) were further verified by retrieving the endoscopy and the surgical summaries, the pathology reports, and the pathology specimens, which were reviewed by one of the

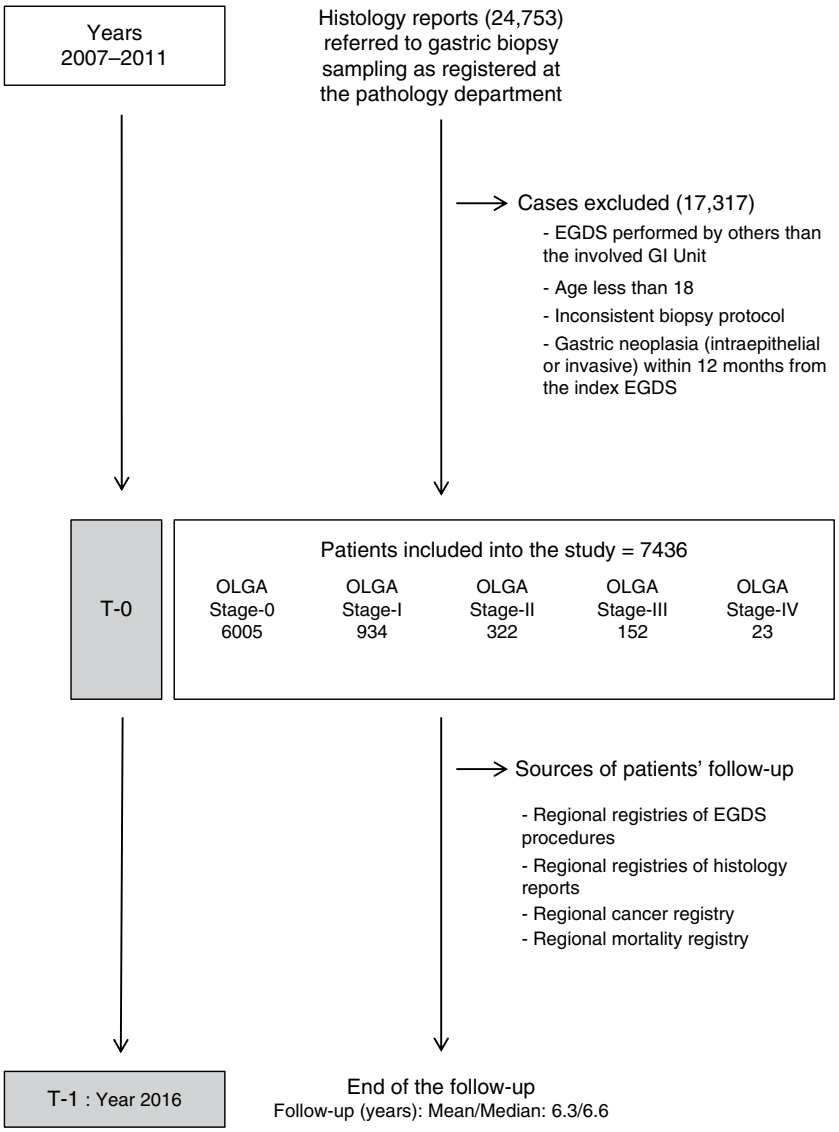

Fig. 1 Patients' selection and follow-up procedure. Each considered patient accumulated person-time for follow-up analysis from the date of enrollment to the date of gastric neoplasia incidence, death, emigration or last available follow-up (i.e., January 31, 2016), whichever came first. The vital status of all patients was assessed through record linkage with the population file of residents, as available from the regional healthcare system

Authors (MR). According to the exclusion criteria (see above), any neoplastic lesion whenever assessed within 12 months from the initial (T-0) endoscopy was considered as prevalent and the patient was excluded from the study. All 28 neoplastic lesions were histologically reconsidered and categorized according to the Padova International classification distinguishing: (1) low-grade intraepithelial neoplasia (LG-IEN); (2) high-grade intraepithelial neoplasia (HG-IEN), and (3) invasive adenocarcinoma (GC) [9].

The interobserver consistency (two internal pathologists (MR, MF)) in assessing the IEN grade was evaluated by reconsidering all the IEN cases that emerged during the follow-up (*k*-statistics value: 0.67, 95%CI = 0.46–0.95) [32].

In all cases of invasive malignancy, both the adenocarcinoma histotype and its pathological stage (TNM staging according to the WHO criteria) were also recorded.

Statistical methods

A linear trend of incidence rate over OLGA stages was assessed by Cochran–Armitage trend test. Multivariate analyses were performed using the Cox proportional-hazards model. Kaplan–Meier analysis was performed to analyze the incidence of neoplasia according to the OLGA stage at the enrollment. All p values are two-sided; p values of less than 0.05 were considered significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

RESULTS

Study population at enrollment (T-0)

The mean and median age of the 7436 patients included in this study were 54 and 55, respectively (patients' distribution by quar-

Table 1 The OLGA (Operative Link on Gastritis Assessment) staging-system for gastritis. The table also reports the score values of atrophy to be applied to both mucosecreting and oxyntic compartments. ATROPHY SCORE: Score 0= no atrophy in any of the specimens obtained from the same compartment; Score 1= atrophy involving 1–30% of the specimens obtained from the same compartment; Score 2= atrophy involving 31–60% of the specimens obtained from the same compartment; Score 3= atrophy involving >60% of the specimens obtained from the same compartment

		CORPUS BIOPSY SPECIMENS Overall atrophy score as assessed in biopsy samples obtained from oxyntic mucosa			
		Stage 0	Stage 1	Stage 2	Stage 3
ANTRUM BIOPSY SPECIMENS Overall atrophy-score as assessed in the biopsy samples obtained from both the antrum and angularis incisura	Score 0	Stage 0	Stage I	Stage II	Stage II
	Score 1	Stage I	Stage I	Stage II	Stage III
	Score 2	Stage II	Stage II	Stage III	Stage IV
	Score 3	Stage III	Stage III	Stage IV	Stage IV

tiles: 18–41 years = 1820 [24.5%]; 42–54 years = 1822 [24.5%]; 55–66 years = 1861 [25%]; >66 years = 1933 [26%]) (Table 2). There were 4106 (55.2%) females.

Based on histology at the enrollment (T-0), 1926 subjects (25.9%) were *H. pylori*-positive. Table 3 shows the distribution of cases by OLGA stage, together with the patients' mean/median age, and the prevalence of *H. pylori* infection. The mean age of patients increased significantly along with the OLGA stage (Pearson's correlation coefficient = 0.95; $p = 0.0123$). When patients were stratified into younger and older than 65 years, neoplastic lesions at the end of the follow-up significantly prevailed in the older age group (univariate analysis: HR = 3.89; $p = 0.0004$).

Table 3 shows the incident neoplastic lesions (T-1: LG-IEN = 17; HG-IEN = 4; invasive GC = 7), stratified by OLGA stage at the entry (T-0), with mean/median age and *H. pylori* status at the time the neoplasia was detected (T-1); the time interval between the patients' enrollment (T-0) and the neoplasia detection is also shown. The overall incidence rate of neoplastic lesions per 10^3/person-years (according to the T-0 OLGA stage) is also shown. The significantly increasing (Cochran–Armitage Trend Test: $p < 0.0001$) rate of incidence by stage highlights a well-defined different risk associated to the low-risk (OLGA stages 0–I–II) versus high-risk (OLGA stages III–IV) stages.

Gastric cancers at the end of the follow-up

At follow-up, seven cases of GC were documented: five were located in the antrum, the other two involved the zone between muco-secreting and oxyntic mucosa. The GC histotype was intestinal in five cases (G1/G2) and diffuse in two. The GCs pathological stage (Table 3) was assessed on endoscopically resected gastric mucosa specimens in three patients (all cases featured intestinal-type GC), and in four patients on the surgical resection (two cases featured prevalent diffuse histotype and two cases of Intestinal type).

Intraepithelial neoplasia (HG-IEN and LG-IEN) as documented at follow-up

Among the four patients with HG-IEN, one was enrolled as OLGA stage II (time interval between enrollment and histological assessment of HG-IEN = 42 months; the patient was *H. pylori*-positive at enrollment and the infection was still present in the biopsy set in which the HG-IEN was assessed). All three remaining HG-IEN cases were enrolled as OLGA III (mean time elapsed between enrollment and HG-IEN detection = 50 months; range = 28–72 months), and *H. pylori* was not detected in either the initial biopsy or in the EMR specimens.

Figure 2 shows the Kaplan–Meier curves of the neoplasia-free proportion by OLGA stage. A significant difference in the incidence of neoplastic events (Log-rank test: $p < .0001$) was associated with OLGA stages 0–I–II versus stages III–IV.

The multivariate analysis including gender, age, OLGA-staging and *H. pylori* status, at the time of enrollment, disclosed that OLGA staging was the only parameter significantly related ($p < 0.0001$) to the neoplastic progression (Table 4).

The hazard ratios for both OLGA stages III and IV (HR = 712.4; 95%CI = 92.5–5484.5; $p < .0001$; HR = 1,450.7; 95%CI = 166.7–12,626.0, respectively; $p < .0001$) significantly associated these two stages to highest risk for cancer development (high-risk OLGA stages).

DISCUSSION

In countries other than Japan and, more recently, South Korea, most gastric cancers are first diagnosed in advanced stage, a harbinger of poor clinical behavior [1].

More than 95% of gastric cancers occur in a background of gastric mucosal atrophy, usually resulting from current or past *H. pylori* infection [33]. Based on the well-established evidence that the severity of mucosal atrophy parallels neoplastic risk, the OLGA-staging system for gastritis bases its assessment of cancer risk on both histological extent and topographic distribution of gastric atrophy. Thus, each stage may be potentially considered for histology-tailored and patient-specific follow-up strategies. While the OLGA system has garnered broad clinical acceptance, no international guidelines currently include the gastritis stage as a discriminant in the timing of the endoscopy follow-up [8, 34, 35].

This long-term follow-up study calculated the incidence of epithelial neoplastic events occurring in the long-term follow-up of

Table 2 Patients by OLGA stage at the enrollment (T-0): gender, age, *Hp*+ve status, and follow-up time

OLGA stages	Number (%)	Prevalence of males	Age; mean/median range; IQR	*Hp*+ve status	Follow-up (years) mean/median
Stage 0	6005 (80.8)	44.8%	52/52; Range = 18–90; IQR = 40–65	24.3%	6.3/6.6
Stage I	934 (12.6)	46.7%	60/63; Range = 20–92; IQR = 51–71	33.8%	6.3/6.6
Stage II	322 (4.3)	42.5%	65/66; Range = 27–87; IQR = 58–74	30.4%	6.3/6.6
Stage III	152 (2.0)	46.1%	67/69; Range = 41–87; IQR = 61–76	32.9%	5.9/6.2
Stage IV	23 (0.3)	52.2%	69/70; Range = 46–88; IQR = 60–81	17.4%	5.3/5.3
TOTAL	7436	44.8% (3330/7436)	54/55; Range = 18–92; IQR = 42–67	25.9%	6.3/6.6

IQR interquartile range, *H+ve H. pylori* positive

Table 3 Patients (7436) stratified by OLGA stage at their enrollment (T-0)

T-0: OLGA stage number of cases (%)	T-1: 28 cases of neoplasia	Time interval between enrollment (T-0) and neoplasia detection (T-1)	T-1: patients' age mean/median (range)	*Hp* status at T-1 (*Hp* status at enrollment = T-0)	Neoplasia: incidence rate 10^3 persons-years (p-years)
Stage 0 6005 (80.8)	LG-IEN = 0	—	—	—	p-years = 37,933 Rate × 10^3 = 0.03
	HG-IEN = 0	—	—	—	
	GC = 1 (p-Stage: I)	25 months	66	*Hp*+ve = 1 (T-0: *Hp*+ve = 1)	
Stage I 934 (12.6)	LG-IEN = 1	57 months	71	*Hp*−ve = 1 (T-0: *Hp*+ve = 1)	p-years = 5903 Rate × 10^3 = 0.34
	HG-IEN = 0	—	—	—	
	GC = 1 (p-Stage: I)	92 months	51	*Hp*+ve = 1 (T-0: *Hp*+ve = 1)	
Stage II 322 (4.3)	LG-IEN = 2	47/50 months	58/58 (50–66)	*Hp*+ve = 1 (T-0: *Hp*+ve = 1) *Hp*−ve = 1 (T-0: *Hp*+ve = 1)	p-years = 7033 Rate × 10^3 = 1.48
	HG-IEN = 1	42 months	63	*Hp*+ve = 1 (T-0: *Hp*+ve = 1)	
	GC = 0	—	—	—	
Stage III 152 (2.0)	LG-IEN = 11	54/62 months	67/72 (48–79)	*Hp*+ve = 2 (T-0: *Hp*+ve = 2) *Hp*−ve = 9 (T-0: *Hp*+ve = 9)	p-years = 890 Rate × 10^3 = 19.1
	HG-IEN = 3	50/51 months	70/70 (64–77)	*Hp*−ve = 3 (T-0: *Hp*−ve = 3)	
	GC = 3 (p-Stage: I, I, IV)	12/18 months	64/61 (51–82)	*Hp*+ve = 2 (T-0: *Hp*+ve = 2) *Hp*−ve = 1 (T-0: *Hp*−ve = 1)	
Stage IV 23 (0.3)	LG-IEN = 3	30/34 months	81/84 (75–85)	*Hp*+ve = 1 (T-0: *Hp*−ve = 1) *Hp*−ve = 2 (T-0: *Hp*+ve = 2)	p-years = 121 Rate × 10^3 = 41.21
	HG-IEN = 0	—	—	—	
	GC = 2 (p-Stage: I, IIa)	19 months	61/61 (55–67)	*Hp*−ve = 1 (T-0: *Hp*+ve = 1) *Hp*−ve = 1 (T-0: *Hp*−ve = 1)	

The table also shows the 28 neoplastic lesions, the patients' mean/median age (years), and the *H. pylori* status as histologically assessed at the end of the follow-up (T-1). *Hp* status at the patients' enrollment (T-0) is shown in brackets
LG-IEN low-grade intraepithelial neoplasia, *HG-IEN* high-grade intraepithelial neoplasia, *GC* gastric cancer, *Hp+ve Hp* positive, *Hp−ve Hp* negative

a series of 7436 consecutive patients who underwent esophagogastroduodenoscopy for the evaluation of dyspepsia, bloating, and epigastric pain and/or discomfort. At the time of the initial endoscopy (T-0), all these patients had a Sydney System-compliant set of gastric biopsies, which was then staged histologically according to the OLGA system. After the initial diagnosis, information on the progression of gastric pathology for all patients was gathered from different official registries of the Regional Healthcare System ((RHS), Fig. 1). This multifaceted information, made possible by the highly structured interconnected RHS, allowed to confidently assume that none of the patients had a diagnosis of any relevant gastric epithelial lesion other than those that have been histologically documented. Even the most capillary registry-based investigation, however, cannot guarantee that neoplastic events occurring in asymptomatic patients who did not seek medical attention may have been missed.

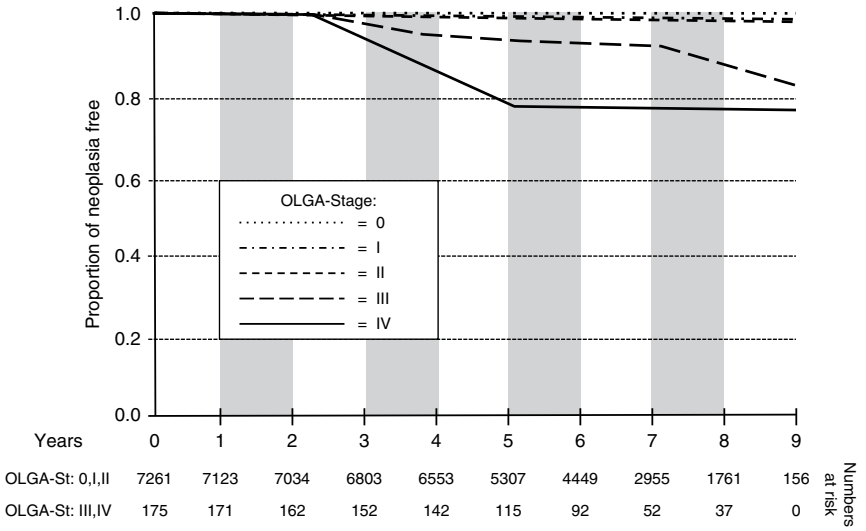

Fig. 2 Kaplan–Meier curves of the neoplasia-free proportion by OLGA stage (OLGA St). A significant difference in the incidence of neoplastic events is associated with OLGA stages 0–I–II versus stages III–IV (Log-rank test: $p < .0001$)

Table 4 Multivariate analysis including all the considered variables: HR for developing neoplastic lesions at follow-up

Variable at the enrollment		Hazard ratio	HR 95% CI	*p* value
Gender	Male versus female	1.65	0.77–3.50	0.17
Age	≥65 versus <65 years	1.16	0.53–2.52	0.72
OLGA stages	0[a]	1	—	—
	I	12.7	1.14–140.7	0.039
	II	54.9	5.63–534.6	<0.0006
	III	712.4	92.5–5484.5	<0.0001
	IV	1,450.7	166.7–12,626.0	<0.0001
Hp status	*Hp*−ve versus *Hp*+ve	0.82	0.34–1.95	0.65

[a][15]

The patient distribution by gastritis stage at enrollment (T-0) was comparable to that reported in other studies conducted both in similar and different epidemiological contexts [14, 15, 19, 20, 25–28, 36, 37].

The number of patients significantly decreased with each increasing stage from 88% at stage 0 to 2.3% at stages III–IV; this pattern is consistent with both the biological concept of multistep gastric oncogenesis (i.e., cancer risk increasing with age) and the epidemiological profile of gastric pre-neoplastic and neoplastic lesions [34, 35, 38]. Furthermore, the mean age of patients steadily increased along with the OLGA stage. Both results confirm age as a risk factor for gastric epithelial neoplastic lesions. Of note, the significance of age ($p < .0001$; as documented in the univariate analysis—data not shown) disappeared in the multivariate testing, being associated in the OLGA staging as a major risk factor.

Six of the 28 incident neoplastic lesions occurred in patients enrolled as OLGA stage 0–I–II. All these six patients were *H. pylori*-positive at T-0, 4/6 still harbored the infection T-1: these findings further support the strategy of primary preventing GC by *H. pylori* eradication.

The incidence of neoplastic lesions varied with the baseline OLGA stage, which reliably differentiated low-risk versus high-risk stages. These findings, further supported by multivariate analysis, emphasize the clinical priority of offering endoscopic follow-up to patients in high-risk OLGA stages (III and IV).

In this series, one invasive gastric carcinoma (p-Stage IV) was diagnosed after 12 months from the initial endoscopy, when the T-0 OLGA stage was III. While a rapidly developing "interval cancer" cannot be excluded, it appears more likely that the neoplastic lesion was missed at the initial endoscopy. This possibility not only supports the unfavorable prognostic meaning of stages III/IV gastritis, but emphasizes the priority to apply high-resolution endoscopy, particularly in patients with high-risk gastritis stages. In the majority of neoplastic lesions, however, the time lapse from the initial OLGA staging to the neoplasia detection was longer than 12 months, but shorter than 3 years. This finding supports the recommendation that for patients with stages III–IV (i.e., antrum-to-corpus spreading gastric atrophy), the 3-year endoscopy-interval, as recommended by current guidelines, is too long, and a 2-year interval should be more cautiously considered [11–13, 39].

Shortcomings of this study include the histology-based *H. pylori* status assessment (which sensitivity is sub-optimal in extensive atrophic-metaplastic lesions), and the lack of reliable information on the eradication therapies (if any) applied in the time interval between T-0 and T-1. Moreover, it is possible, albeit unlikely, that some early (clinically unsuspected) neoplastic lesions at T-1 may have been missed.

In summary, this long-term follow-up study of an epidemiologically stable cohort of 7436 patients demonstrated that OLGA stag-

ing is a reliable predictor of the risk for gastric neoplastic lesions, including gastric cancer. Among *H. pylori*-positive patients, even those with a low-risk OLGA stage, the persistence of the infection may promote neoplastic progression, further supporting the need for both eradication and the non-invasive assessment of its success. Among patients with OLGA stage III/IV, the eradication of the *H. pylori* infection does not necessarily reverse the cancer risk; in these patients high-resolution endoscopy is recommended to reduce the risk of missing small neoplastic foci [40–44].

ACKNOWLEDGEMENTS

The authors are indebted to Ms. Suzanne Ridner for proofing and editing the manuscript.

CONFLICTS OF INTEREST

Guarantor of the article: Massimo Rugge.

Specific author contributions: Study concept and design: MR; acquisition of data: MF, EV, IC; ES, FF; analysis and interpretation of data: MR, RMG, MZ, SG, PM; drafting of the manuscript: MR, RMG; statistical analysis: SG, MZ; obtained funding: MR.

Financial support: This work was partly supported by a grant of the Italian Association for Cancer Research (AIRC Regional grant n. 6421 to MR).

Potential competing interests: None

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Gastric mucosal atrophy is the cancerization field in which most gastric cancers occur.
- ✓ Endoscopy follow-up protocols for atrophic gastritis are debated.
- ✓ Based on extension and topography of the atrophic-metaplastic changes, the histological staging of gastritis is a reliable predictor of gastric cancer risk.

WHAT IS NEW HERE

- ✓ Gastritis staging ranks the atrophy-associate risk for gastric cancer into different classes.
- ✓ Gastritis staging is critical in designing patient-tailored endoscopy follow-up protocols aimed at the secondary prevention of gastric cancer.

REFERENCES

1. Colquhoun A, Arnold M, Ferlay J, et al. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015;64:1881–88.
2. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385:977–1010.
3. Correa P. The biological model of gastric carcinogenesis. IARC Sci Publ. 2004;157:301–10.
4. Agreus L, Kuipers EJ, Kupcinskas L, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand J Gastroenterol. 2012;47:136–47.
5. Park YH, Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. J Cancer Prev. 2015;20:25–40.
6. Graham DY. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology. 2015;148:719–31.e3.
7. Lee YC, Chiang TH, Chou CK, et al. Association between helicobacter pylori eradication and gastric cancer incidence: a systematic review and meta-analysis. Gastroenterology. 2016;150:1113–24.e5.
8. Rugge M, Genta RM, Graham DY, et al. Chronicles of a cancer foretold: 35 years of gastric cancer risk assessment. Gut. 2016;65:721–5.
9. Rugge M, Correa P, Dixon MF, et al. Gastric dysplasia: the Padova international classification. Am J Surg Pathol. 2000;24:167–76.
10. Rugge M, Cassaro M, Di Mario F, et al. The long term outcome of gastric non-invasive neoplasia. Gut. 2003;52:1111–6.
11. Dinis-Ribeiro M, Areia M, de Vries AC, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012;44:74–94.
12. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 2015;64:1353–67.
13. Zagari RM, Romano M, Ojetti V, et al. Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015. Dig Liver Dis. 2015;47:903–12.
14. Rugge M, de Boni M, Pennelli G, et al. Gastritis OLGA-staging and gastric cancer risk: a twelve-year clinico-pathological follow-up study. Aliment Pharmacol Ther. 2010;31:1104–11.
15. Rugge M, Genta RM. Staging and grading of chronic gastritis. Hum Pathol. 2005;36:228–33.
16. Rugge M, Pennelli G, Pilozzi E, et al. Gastritis: the histology report. Dig Liver Dis. 2011;43(Suppl 4):S373–84.
17. Rugge M, Meggio A, Pravadelli C et al. Gastritis staging in the endoscopic follow-up for the secondary prevention of gastric cancer: a 5-year prospective study of 1755 patients. Gut. 2018. https://doi.org/10.1136/gutjnl-2017-314600
18. Mescoli C, Gallo Lopez A, Taxa Rojas L, et al. Gastritis staging as a clinical priority. Eur J Gastroenterol Hepatol. 2018;30:125–9.
19. 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;71:1150–8.
20. Satoh K, Osawa H, Yoshizawa M, et al. Assessment of atrophic gastritis using the OLGA system. Helicobacter. 2008;13:225–9.
21. Marcos-Pinto R, Carneiro F, Dinis-Ribeiro M, et al. First-degree relatives of patients with early-onset gastric carcinoma show even at young ages a high prevalence of advanced OLGA/OLGIM stages and dysplasia. Aliment Pharmacol Ther. 2012;35:1451–9.
22. Cho SJ, Choi IJ, Kook MC, et al. Staging of intestinal- and diffuse-type gastric cancers with the OLGA and OLGIM staging systems. Aliment Pharmacol Ther. 2013;38:1292–302.
23. Nam JH, Choi IJ, Kook MC, et al. OLGA and OLGIM stage distribution according to age and Helicobacter pylori status in the Korean population. Helicobacter. 2014;19:81–9.
24. Bornschein J, Dingwerth A, Selgrad M, et al. Adenocarcinomas at different positions at the gastro-oesophageal junction show distinct association with gastritis and gastric preneoplastic conditions. Eur J Gastroenterol Hepatol. 2015;27:492–500.
25. Ben Slama S, Ben Ghachem D, Dhaoui A, et al. Helicobacter pylori gastritis: assessment of OLGA and OLGIM staging systems. Pan Afr Med J. 2016;23:28.
26. Zhou Y, Li HY, Zhang JJ, et al. Operative link on gastritis assessment stage is an appropriate predictor of early gastric cancer. World J Gastroenterol. 2016;22:3670–8.
27. Wang X, Lu B, Meng L, et al. The correlation between histological gastritis staging- 'OLGA/OLGIM' and serum pepsinogen test in assessment of gastric atrophy/intestinal metaplasia in China. Scand J Gastroenterol. 2017;52:822–7.
28. Kim YI, Kook MC, Cho SJ et al. Effect of biopsy site on detection of gastric cancer high-risk groups by OLGA and OLGIM stages. Helicobacter. 2017;22. https://doi.org/10.1111/hel.12442.
29. Rugge M, Genta RM, Di Mario F, et al. Gastric cancer as preventable disease. Clin Gastroenterol Hepatol. 2017;15:1833–43.
30. den Hoed CM, Holster IL, Capelle LG, et al. Follow-up of premalignant lesions in patients at risk for progression to gastric cancer. Endoscopy. 2013;45:249–56.
31. Rugge M, Correa P, Di Mario F, et al. OLGA staging for gastritis: a tutorial. Dig Liver Dis. 2008;40:650–8.

32. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159–74.
33. Correa P, Piazuelo MB. *Helicobacter pylori* infection and gastric adenocarcinoma. US Gastroenterol Hepatol Rev. 2011;7:59–64.
34. Rugge M, Capelle LG, Cappellesso R, et al. Precancerous lesions in the stomach: from biology to clinical patient management. Best Pract Res Clin Gastroenterol. 2013;27:205–23.
35. Rugge M, Capelle LG, Fassan M. Individual risk stratification of gastric cancer: evolving concepts and their impact on clinical practice. Best Pract Res Clin Gastroenterol. 2014;28:1043–53.
36. Rugge M, Meggio A, Pennelli G, et al. Gastritis staging in clinical practice: the OLGA staging system. Gut. 2007;56:631–6.
37. Molaei M, Ehtiati A, Mashayekhi R, et al. Gastric atrophy: use of OLGA staging system in practice. Gastroenterol Hepatol Bed Bench. 2016;9:25–9.
38. Rugge M, Leandro G, Farinati F, et al. Gastric epithelial dysplasia. How clinicopathologic background relates to management. Cancer. 1995;76:376–82.
39. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. Gut. 2017;66:6–30.
40. Quach DT, Le HM, Nguyen OT, et al. The severity of endoscopic gastric atrophy could help to predict Operative Link on Gastritis Assessment gastritis stage. J Gastroenterol Hepatol. 2011;26: 281–5.
41. Rugge M, Dinis-Ribeiro M. Letter: gastric atrophy assessment-merging serology, endoscopy and histology in clinical practice. Aliment Pharmacol Ther. 2018;47:151–2.
42. Rugge M. Gastric cancer risk in patients with *Helicobacter pylori* infection and following its eradication. Gastroenterol Clin North Am. 2015;44:609–24.
43. Rugge M, de Boni M, Pennelli G, Mescoli C, Graham DY. OLGA can guard the barn. Am J Gastroenterol. 2009;104:3099.
44. Saka A, Yagi K, Nimura S. OLGA- and OLGIM-based staging of gastritis using narrow-band imaging magnifying endoscopy. Dig Endosc. 2015;27:734–41.