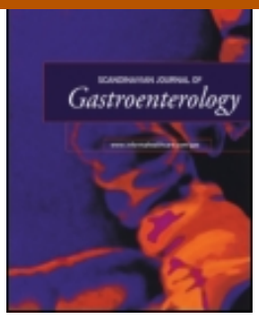

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ORIGINAL ARTICLE

Occurrence of gastric cancer and carcinoids in atrophic gastritis during prospective long-term follow up

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Abstract

Objective. Atrophic gastritis (AG) is a risk condition for gastric cancer and type I gastric carcinoids. Recent studies assessing the overall risk of gastric cancer and carcinoids in AG at long-term follow up are lacking. This study aimed to investigate in a prospective cohort of AG patients the occurrence of gastric cancer and carcinoids at long-term follow up. ***Methods.*** A total of 200 AG patients from a prospective cohort (67% female, median age 55 years) with a follow up of 7.5 (range: 4–23.4) years were included. Inclusion criteria were presence of AG and at least one follow-up gastroscopy with biopsies at ≥4 years after AG diagnosis. Follow-up gastroscopies at 4-year intervals were performed. ***Results.*** Overall, 22 gastric neoplastic lesions were detected (crude incidence 11%). Gastric cancer was diagnosed in four patients at a median follow up of 7.2 years (crude incidence 2%). Eleven type I gastric carcinoids were detected at a median follow up of 5.1 years (crude incidence of 5.5%). In seven patients, six low-grade and one high-grade dysplasia were found. The annual incidence rate person-year were 0.25% (95% confidence interval [CI]: 0.067–0.63%), 0.43% (95% CI: 0.17–0.89%), and 0.68% (95% CI: 0.34–1.21%) for gastric cancer, dysplasia, and type I-gastric carcinoids, respectively. The incidence rates of gastric cancer and carcinoids were not different ($p = 0.07$). ***Conclusion.*** This study shows an annual incidence rate of 1.36% person-year for gastric neoplastic lesions in AG patients at long-term follow up. AG patients are similarly exposed to gastric cancer and type I gastric carcinoids.

Key Words: *atrophic gastritis, follow up, gastric cancer, pernicious anemia, type I gastric carcinoids*

Introduction

Atrophic gastritis (AG) is characterized by the loss of gastric glands replaced by connective tissue or glandular structures inappropriate for location giving arise to nonmetaplastic or metaplastic atrophy and – as a consequence – to hypochlorhydria and hypergastrinemia [1]. Late-stage AG is often associated with pernicious anemia [2]. AG is considered a precursor condition for gastric cancer [3,4]. At follow-up periods ranging from 1 to 16 years, a varying progression rate of AG to gastric cancer up to 2% per year has been reported [5–7]. A recent systematic review showed, in AG patients with pernicious anemia, a pooled gastric cancer incidence rate of 0.3% person-year and an estimated sevenfold relative risk of gastric cancer [8]. Gastric cancer is still the fourth most common cancer worldwide and the second cause of cancer-related death [9]. Gastric carcinogenesis probably involves a multistep progression from *Helicobacter pylori*-related chronic inflammation, to atrophy, intestinal metaplasia, dysplasia, and, finally, intestinal-type gastric cancer [3]. In parallel, the concept of "gastritis of the carcinoma phenotype" proposes that the corpus-predominant gastritis increases the risk of gastric cancer [10–12], likely due to changes in the

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intragastric milieu as increased pH, reduced ascorbic acid, and scavenging of nitrites and other potential carcinogenic substances [13,14].

In patients with AG, type I gastric carcinoids may also arise. These tumors are well differentiated with low proliferative index and a generally benign behavior, and constitute up to 80% of all gastric carcinoids [15–17]. A major pathogenetic factor for type I gastric carcinoids is hypergastrinemia due to AG. Gastrin acts as a growth factor for enterochromaffin-like cells, which in AG are chronically induced to proliferate, and, through a multistep process passing from hyperplasia to dysplasia, carcinoid may develop [17–19]. Data on long-term incidence of type I gastric carcinoids are scanty [20–22]. A recent cohort study reported an annual incidence rate of 0.4% for type I gastric carcinoids [23], whereas an older study reported an annual incidence rate of 2%, observing 8 new cases of type I gastric carcinoids in 416 patient-years [21]. In the above-cited study, pernicious anemia was present in almost 50% of patients with type I gastric carcinoids [23], whereas previous studies exclusively included patients with this condition [21,22,24–26].

In patients with AG, the need and cost-effectiveness of regular endoscopic follow up for gastric cancer surveillance is not definitely established. Recent European guidelines recommend a scheduled surveillance for gastric cancer for those AG patients who have extensive – that is, both antrum and gastric body – AG or intestinal metaplasia [27]. In a previous study, a follow-up interval of 4 years after diagnosis was shown to be satisfactory for detection of potential neoplastic lesions in AG patients [28]. IN regard to surveillance for type I gastric carcinoids, indications are even more uncertain. A recent study on endoscopic management of these tumors, reported that for AG patients without recurring type I gastric carcinoids, endoscopic controls might be planned yearly in the early follow up but can probably become less intensive with endoscopic controls every 4 years according to AG screening for gastric cancer risk [29]. It has been argued that to evaluate the exact value of surveillance in AG patients and establish follow-up frequencies, more precise data on the occurrence of gastric neoplastic lesions, preferably obtained in large prospective studies with adequate follow up, are needed [30].

The overall risk of gastric cancer and carcinoids together has been investigated only in pernicious anemia patients many years ago [21,22], and recent studies assessing the overall risk of gastric neoplastic lesions in AG at long-term follow up are lacking. This study aimed to investigate the occurrence of gastric cancer and carcinoids in a prospective cohort of patients with AG at long-term follow up from 4 years upwards.

Methods

Study population and design

In this study, 200 patients (67% female, median age 55 years, range 22–84 years) with AG with a median follow up of 7.5 years (range 4–23.4 years) were included. Inclusion criteria were the presence of AG and at least one follow-up investigation by gastroscopy with biopsies at an interval of at least 4 years after first diagnosis of AG. Exclusion criteria were severe chronic comorbidity, making follow-up gastroscopies not feasible, and the presence of gastric cancer at the time of diagnosis of AG.

This study population derived from a prospective cohort of patients with AG diagnosed between 1992 and 2009, which is included in a surveillance program for gastric neoplastic lesions [7,23].

The eligible patients numbered 378, of whom during follow up 8 (2.1%) died for causes not related to gastric cancer, 2 (0.5%) had gastric surgery for other reasons, and 168 (44.4%) were lost at follow up (not retraceable 30.1%, refused 14.3%). Thus, overall 178 (47.1%) patients of the baseline population dropped out during follow up and the final follow-up population comprised 200 (52.9%) patients with AG. The main baseline features of the study population are given in Table I.

At diagnosis of AG, all patients underwent a clinical interview based on a structured questionnaire to assess personal and clinical data, family history for gastric cancer and lifestyle items. All patients were informed by the way of a specific information sheet about the increased risk of gastric cancer and type I gastric carcinoid associated with AG and about the need to undergo regular follow up by gastroscopy (see management and follow-up protocol section). The assumption of proton pump inhibitors was carefully checked and was withdrawn.

At the time of diagnosis of AG, among the 200 included patients, 4 (2%) type I gastric carcinoids and 7 (3.5%) noninvasive neoplasias were detected. In detail, three of the four patients with gastric carcinoids were female, aged between 40 and 77 years (median 56.5 years). Three of them had intramucosal gastric carcinoids and in the fourth patient the gastric carcinoid was a polyp <1 cm which was removed by endoscopic polypectomy. Five (71.4%) of the seven patients with noninvasive neoplasias were female, aged between 51 and 71 years (median 61 years). All lesions were low-grade dysplasia, five of them localized in the antral mucosa without endoscopic lesions and two of them were corporal adenomatous polyps (<1 cm) removed by endoscopic polypectomy.

From all patients a written consent was obtained.

Table I. Main features of the 200 patients with atrophic gastritis.

Female gender	134 (67)
Age, years, median (range)	55 (22–84)
Overall follow up, years, median (range)	7.5 (4–23.4)
Overall number of follow-up investigations, median (range)	4 (2–12)
Smoking habit	78 (39)
Presence of pernicious anemia	105 (52.5)
First degree family history for gastric cancer	21 (10.5)
Sydney scores of corporal mucosa	
Atrophy	
Mild	41 (20.5)
Moderate	40 (20.0)
Severe	119 (59.5)
Intestinal metaplasia	
Absent	37 (18.5)
Mild	66 (33.0)
Moderate	66 (33.0)
Severe	31 (15.5)
Helicobacter pylori	
Absent	177 (88.5)
Mild	13 (6.5)
Moderate	6 (3.0)
Severe	4 (2.0)
Sydney scores of antral mucosa	
Atrophy	
Absent	160 (80.0)
Mild	29 (14.5)
Moderate	9 (4.5)
Severe	2 (1.0)
Intestinal metaplasia	
absent	171 (85.5)
Mild	18 (9.0)
Moderate	10 (5.0)
Severe	1 (0.5)
Helicobacter pylori	
Absent	184 (92.0)
Mild	12 (6.0)
Moderate	3 (1.5)
Severe	1 (0.5)

Data are expressed as total number (%), when not otherwise reported.

Diagnostic criteria for AG and gastric neoplastic lesions

The diagnosis of AG was based on the histological confirmation of gastric body atrophy and the presence of fasting gastrin above upper normal values [31]. All patients underwent gastroscopy with three biopsies taken from the gastric antrum (within 3 cm of the pyloric ring, lesser and greater curve, anterior or posterior wall) and three biopsies from the mid-body along the greater curve [15]. In case of lesion, additional biopsies were obtained. The specimens were formalin-fixed and routinely processed. About 5 μm thick mucosal gastric sections were stained with hematoxylin-eosin for routine examination and Giemsa staining for *H. pylori*.

According to the updated Sydney System, gastric body atrophy was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands; this variable was graded on a four-grade scale represented by absence of replacement (score 0), replacement to a mild degree (score 1), moderate degree (score 2), or severe degree (score 3), as previously reported [32]. Atrophy of the antral mucosa was defined as focal or complete disappearance of antral glands or their replacement by intestinal metaplastic epithelium [31].

Serological assays were performed in every patient, evaluating: fasting serum gastrinemia (normal value < 40 pg/ml) and immunoglobulin (Ig)G *H. pylori* antibodies (normal value < 21 UI/ml). Gastrin was measured by radioimmunoassay, whereas *H. pylori* antibodies IgG were measured by an enzyme-linked immunosorbent assay commercial kit (GAP test IgG; Biorad, Milan, Italy). Anemia pattern was also assessed, evaluating hemoglobin, mean corpuscolar volume (MCV), ferritin, and vitamin B_{12} values. Pernicious anemia was defined as low hemoglobin concentration, MCV > 100 fl together with low B_{12} vitamin levels, responding to intramuscular B_{12} vitamin treatment [33]. Iron-deficiency anemia was defined as low hemoglobin concentration, MCV < 80 fl, and ferritin < 30 ng/ml [33].

The definitions of gastric neoplastic lesions (noninvasive neoplasia and gastric cancer) were based on the Padova International Classification and WHO guidelines [34,35]. Diagnosis of type I gastric carcinoid was performed when enterochromaffin-like cells cell proliferation was >500 μ [36], classified according to WHO 2010 criteria [16].

H. pylori status and treatment

H. pylori status was considered as positive when a positive *H. pylori* IgG titer was detected and/or bacteria were revealed at histology by Giemsa stain [31]. Bismuth-based triple regimen eradication therapy was prescribed in the case of *H. pylori* positivity and, after 6 months, the absence of *H. pylori* at histology and a decrease by at least 50% in the initial titer of *H. pylori* IgG was the criterion for the successful cure of infection [37]. Overall, 97 out of the 112 (86.6%) *H. pylori*-positive patients were cured of infection.

Management and follow-up protocol

As shown in (Figure 1), in general, the first follow-up gastroscopy was scheduled 4 years after diagnosis of AG during which the same baseline bioptic sampling was repeated [7,28]. Subsequent follow-up investigations were scheduled at 4-year intervals with same bioptic sampling. Endoscopic histological

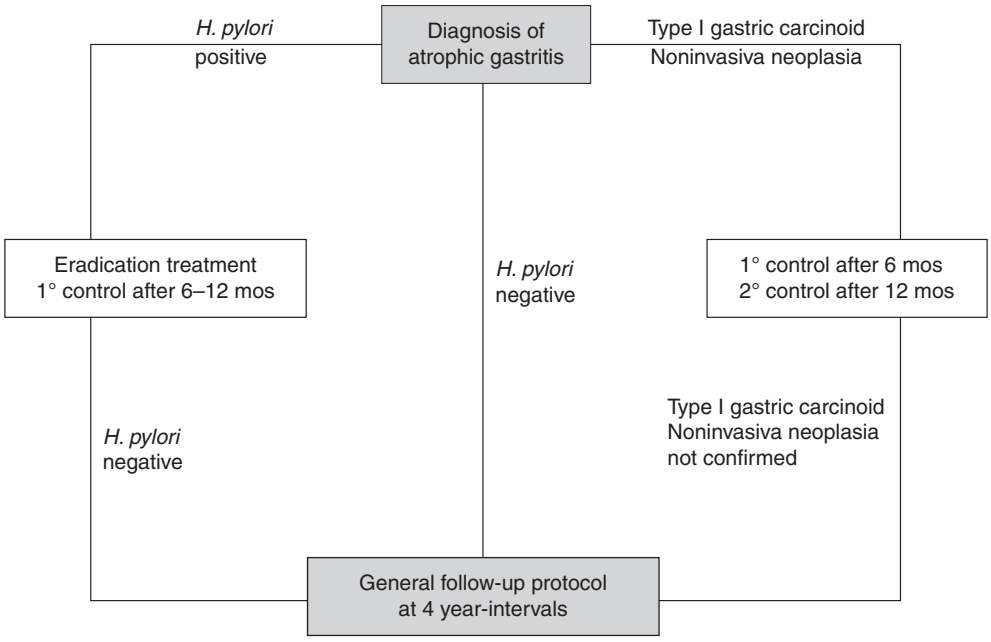

Figure 1. Illustration showing the follow-up protocol. Abbreviation: mos = Months.

investigations at shorter intervals earlier than 4 years after first diagnosis of AG were performed in the case of *H. pylori* eradication treatment and diagnosis of gastric neoplastic lesions. In the case of *H. pylori* eradication treatment, gastroscopy/histology was performed at 6 months to evaluate the efficacy of cure and then patients were monitored by the general follow-up protocol. If noninvasive neoplasia was detected, an extensive bioptic sampling of at least 10 biopsies of the gastric mucosa was taken after 6 and 12 months for low-grade noninvasive neoplasia and after 3, 6, and 12 months for high-grade noninvasive neoplasia [7]. If noninvasive neoplasia was not confirmed at two following gastroscopies, patients were followed up by the general follow-up protocol. When gastric polyps were detected, polypectomy was performed. Polypoid lesions up to 5 mm were removed by forceps; otherwise, an electrocautery snare was used. In the case of a histological diagnosis of gastric cancer, the indication for mucosectomy and/or surgery was evaluated. After first diagnosis of type I gastric carcinoids, gastroscopy with extensive bioptic sampling after 6 and 12 months was performed. If type I gastric carcinoid was not confirmed at two following gastroscopies, patients were followed up by the general follow-up protocol. All patients with a diagnosis of type I gastric carcinoids underwent at least one imaging procedure for the tumor staging (CT-scan, Octreoscan, Gallium-68 PET scan) [23,29]. Patients with type I gastric carcinoids were managed by endoscopic polypectomy and/or endoscopic/histological surveillance and did not undergo medical treatments.

However, at any time, when patients referred the onset of alarm symptoms, such as dysphagia, repeated vomiting, weight loss, dyspepsia, and/or recent onset or worsening of iron-deficiency anemia, gastroscopy was immediately performed.

Data analysis and statistical evaluation

The occurrence of new cases of gastric cancer and type I gastric carcinoids in AG patients were evaluated after a follow up of at least 4 years up to the longest follow up available. Data were expressed as crude incidence and incidence rate (person-years).

Standard descriptive statistics were expressed as medians and ranges or absolute counts and percentages. Mann–Whitney and chi-square tests were used when appropriate. Univariate analysis was performed to identify patients' features associated with the presence of gastric neoplastic lesions at long-term follow up. Multivariate Cox-regression analysis was performed to identify risk factors for gastric neoplastic lesions. The incident gastric neoplastic lesions were coded with value 1 in the binary-dependent variable. For gastric cancer and dysplasia, the following features were considered as covariates: age >50 years, gender, family history for gastric cancer, the presence of concomitant antral and corporal atrophy, the presence of intestinal metaplasia in the antrum, the presence of *H. pylori* in the corpus, treatment for

H. pylori, and the number of follow-up investigations. For gastric carcinoids, the following features were considered as covariates: gender, age <50 years, the presence of pernicious anemia, the presence of autoimmune diseases, and fasting gastrin 12-fold over normal values; however, COX-regression analysis could not be performed since the covariate pernicious anemia was present in all patients with gastric carcinoids. For each covariate, the hazard ratio (HR) and 95% confidence intervals (CIs) are reported. Intervals between initial AG diagnosis and diagnosis of gastric neoplastic lesions were analyzed by Kaplan–Meier analysis. A p-Value of <0.05 was considered statistically significant. Statistical analyses were run using a dedicated software (MedCalc Software, Mariakerke, Belgium, version 12).

Results

During an overall follow up from 4 to 23.4 years (median 7.5 years) among the 200 included AG patients, 22 gastric neoplastic lesions were detected, thus resulting in an overall crude incidence of 11%. These lesions were diagnosed in 19 (9.5%) patients. In one female patient, first a type I gastric carcinoid was detected at 3.5 years and subsequently a gastric cancer occurred at 5.1 years. In another female patient, a type I gastric carcinoid was detected at 10.3 years, which recurred at 12 years, and subsequently a gastric cancer was diagnosed at 12.5 years.

In Table II, details of patients with gastric neoplastic lesions are shown. Briefly, gastric cancer was diagnosed in four patients (2 females, aged from

Table II. Main features of atrophic gastritis patients who developed gastric neoplastic lesions at follow up from 4 years upwards.

Age, years	Gender	Endoscopically visible lesion	Site	Histology	Occurrence (years)	Treatment	TNM staging	Outcome
Gastric cancer								
40	Female	No (random biopsies)	Body	Diffuse signet-ring cells gastric cancer	12.5	Total gastrectomy	G1N0M0	Free GNL
77	Male	Ulcer-like 3 cm	Antrum	Intestinal-type adenocarcinoma	6.8	Palliative	G1N0M0	Dead
51	Male	Ulcer-like 5 cm	Antrum	Undifferentiated gastric cancer	7.1	Palliative	G3N1M0	Dead
49	Female	No (random biopsies)	Antrum	Intestinal-type adenocarcinoma	5.1	Total gastrectomy	G1N0M0	Free GNL
Gastric dysplasia								
56	Male	Multiple polyps <1 cm	Antrum	Low-grade dysplasia	4.9	Polypectomy	NA	Free GNL
64	Female	Irregular mucosa	Antrum	High-grade dysplasia	13.6	Partial gastrectomy	NA	Free GNL
65	Male	No (random biopsies)	Antrum	Low-grade dysplasia	4.8	Monitoring	NA	Free GNL
58	Female	Single polyp 4 cm	Body	Low-grade dysplasia	19.7	ESD	NA	Free GNL
58	Female	No (random biopsies)	Antrum	Low-grade dysplasia	4.1	Monitoring	NA	Free GNL
68	Male	No (random biopsies)	Antrum	Low-grade dysplasia	4.1	Monitoring	NA	Free GNL
51	Female	No (random biopsies)	Antrum	Low-grade dysplasia	6.3	Monitoring	NA	Free GNL
Gastric carcinoids								
40	Female	Single polyp <1 cm 2 polyps <1 cm	Fundus Body	Type I gastric carcinoid Type I gastric carcinoid	10.3 12.0	Polypectomy Polypectomy	NA	GC at 12.5 years, surgery, alive
59	Female	2 polyps <1 cm	Body	Type I gastric carcinoid	4.0	Polypectomy	NA	Free GNL
23	Female	Single polyp 1 cm	Body	Type I gastric carcinoid	4.1	Polypectomy	NA	Free GNL
65	Female	No (random biopsies)	Body	Type I gastric carcinoid	4.2	Monitoring	NA	Free GNL
46	Male	Single polyp <1 cm	Body	Type I gastric carcinoid	6.1	Polypectomy	NA	Free GNL
54	Female	No (random biopsies)	Body	Type I gastric carcinoid	8.5	Monitoring	NA	Free GNL
69	Male	Single polyp <1 cm	Body	Type I gastric carcinoid	4.0	Polypectomy	NA	Free GNL
47	Male	No (random biopsies)	Fundus	Type I gastric carcinoid	5.5	Monitoring	NA	Free GNL
34	Female	Single polyp <1 cm	Fundus	Type I gastric carcinoid	15.6	Polypectomy	NA	Free GNL
49	Female	Single polyp <1 cm	Body	Type I gastric carcinoid	4.0	Polypectomy	NA	GC at 5.1 years, surgery, alive

Abbreviations: ESD: Endoscopic submucosal dissection; Free GNL: Free of gastric neoplastic lesions; GC: Gastric cancer; NA: Not applicable; TNM: T
umor nodes metastasis.

40 to 77 years, median age 50 years), thus resulting in a crude incidence rate of 2%. The gastric cancers occurred at a median follow up of 7.2 years (range 5.1 to 12.5 years) in respect to first diagnosis of AG. All but three lesions were localized in the gastric antrum and one was in the body. In regard to histology, two cancers were intestinal-type adenocarcinomas, one was an undifferentiated gastric cancer and the fourth was a diffuse signet-ring cell gastric cancer. In regard to outcome, two patients underwent gastric surgery and are alive. In the other two patients the outcome was fatal: in one patient neither surgery nor other treatments were feasible due to comorbidities and the other patient experienced a fatal progression of disease notwithstanding gastric surgery and subsequent medical therapy.

Eleven type I gastric carcinoids were detected in 10 patients (9 females, aged from 23 to 69 years, median age 48 years) with a crude incidence rate of 5.5%. The gastric carcinoids were diagnosed at a median follow up of 5.1 years (4–15.6 years) in respect to first diagnosis of AG. In eight cases, the type I gastric carcinoid presented as a gastric polyp localized in the body (n = 5) or fundus (n = 3) was removed by polypectomy, in the remaining two cases the type I gastric carcinoids were detected by random biopsies in the fundic mucosa.

In two patients, during further follow up (12.5 and 5.1 years), a gastric cancer was diagnosed.

In the remaining patients (n = 8) no recurrence of new type I gastric carcinoid or other gastric neoplastic lesions was observed and, at the longest follow up, they are all free of neoplastic lesions (median 5.9 years, range 4–15.5 years).

In seven patients (3 females, aged from 51 to 68 years, median age 58 years), six low-grade gastric dysplasias and one high-grade dysplasia were found. These dysplastic lesions occurred at a median follow up of 7.7 years (range 3.8–19.7 years). All these lesions were localized in the gastric antrum; in three cases, the dysplastic lesions were presenting as polyps, in the remaining cases they were localized on an endoscopically normal appearing mucosa and were detected on random bioptic samples. In regard to outcome, after endoscopic removal of polyps and monitoring with random biopsies at the longest follow up of 11.8 years (range 4.1–19.5 years), in none of these cases a new low-grade or high-grade dysplasia recurred neither a type I gastric carcinoid occurred. The one patient with the high-grade dysplasia underwent partial gastrectomy and is alive.

Given the study population of 200 AG patients with an overall observation period of 1619.3 years, the annual incidence rate person-year can be calculated as 0.25% (95% CI: 0.067–0.63%), 0.43% (95% CI: 0.17–0.89%), and 0.68% (95% CI: 0.34–1.21%) for gastric cancer, gastric dysplasia, and type I gastric carcinoids, respectively. The incidence rates of gastric cancer and gastric carcinoids were similar and not statistically different from each other ($p = 0.0707$). For all gastric neoplastic lesions taken together, the annual incidence rate person-year can be calculated as 1.36% (95% CI: 0.85–2.06%).

Hypothetically assuming that first follow up was scheduled at 3 years according to MAPS guidelines, four more gastric neoplastic lesions would have been included (one gastric carcinoid and three gastric dyplasias) and this would have increased the overall number of detected gastric neoplastic lesions to 26 and the annual incidence rate person-year for all gastric neoplastic lesions to 1.61% (95% CI: 1.05–2.35).

Risk factors for gastric cancer and carcinoids and survival by Kaplan–Meier curves

At univariate analysis, patients who developed gastric cancer or dysplasia at follow up were different from those free of these lesions for the presence of concomitant antral and corporal atrophy (58.3% vs. 14.9%, $p < 0.001$), the presence of intestinal metaplasia in the antrum (41.7% vs. 10.3%, $p < 0.01$), and the presence of *H. pylori* in corporal mucosa (33.3% vs. 9.8%, $p < 0.05$), whereas the presence of pernicious anemia, positive family history for gastric cancer, age >50 years, gender, smoking habit or cure of *H. pylori*

Table III. Risk factors for progression to gastric cancer and/or dysplasia in multivariate Cox-regression analysis.

Baseline	HR multivariate	95% CI
Gender		
Male	1.0	1.0
Female	0.8	0.2–2.7
Age		
<50 years	1.0	1.0
>50 years	3.1	0.6–14.8
Presence of concomitant antral and corporal atrophy		
No	1.0	1.0
Yes	7.2	0.7–68.4
Presence of antral intestinal metaplasia		
No	1.0	1.0
Yes	1.2	0.1–12.3
More than 5 follow-up investigations		
No	1.0	1.0
Yes	2.7	0.6–11.5
Presence of *H. pylori* in the corporal mucosa		
No	1.0	1.0
Yes	**8.05**	**1.5–43.3**
Cure of *H. pylori* infection		
No	1.0	1.0
Yes	0.3	0.1–1.2

Significant risk factors are in bold typeface.
Abbreviations: CI = Confidence interval; HR = Hazard ratio.

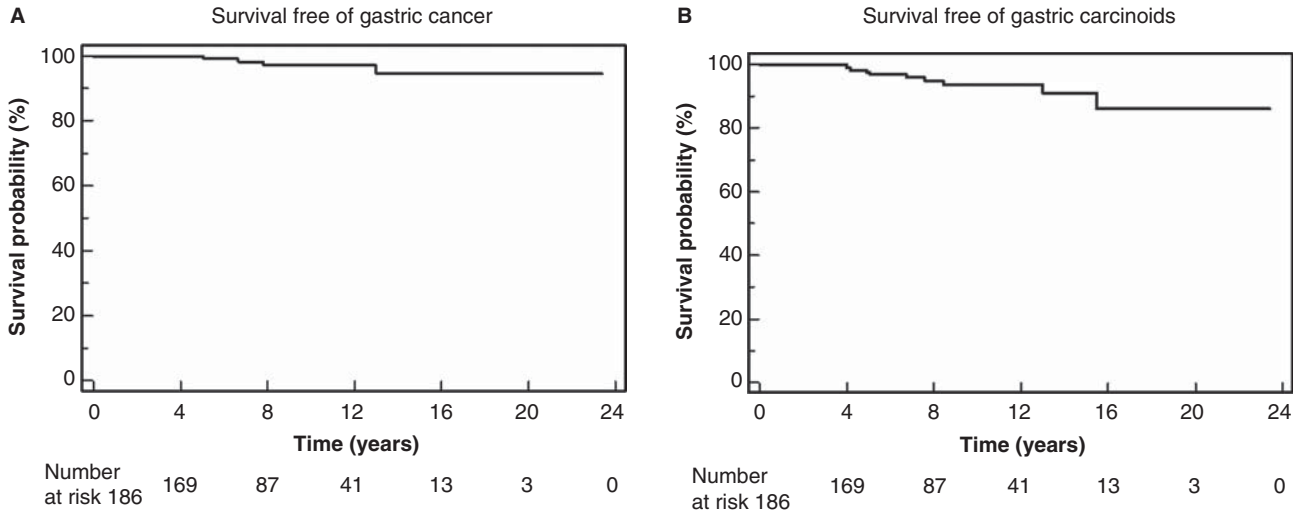

Figure 2. Kaplan–Meier survival curves showing the survival time in years free of gastric cancer (A) and free of gastric carcinoids (B). Baseline cumulative hazard function.

were not different between the two groups. The number of follow-up investigations was higher in the group with lesions ($p < 0.001$). As shown in (Table III), the presence of *H. pylori* in the gastric corpus is a risk factor for gastric cancer and dysplasia (Cox regression analysis: HR 8.05 (95%CI 1.5 to 43.3)).

Performing a subgroup analysis per first-degree family history for gastric cancer, it emerged that gastric neoplastic lesions were more frequent (nearly two-fold) among patients with positive family history compared to those without first-degree relatives with gastric cancer, albeit statistical significance was not reached (23.5% vs. 12.6%, $p = 0.4867$).

Table IV. Retrospective *post-hoc* analysis of OLGA and OLGIM staging system.

	Presence of gastric cancer or dysplasia; $n = 11$	Absence of gastric cancer or dysplasia; $n = 189$	p
OLGA staging			0.0141 (chi-square test for trend)
Stage 0	0	0	
Stage 1	2 (18.2)	37 (19.6)	
Stage 2	4 (36.3)	131 (69.3)	
Stage 3	3 (27.3)	15 (7.9)	0.0046
Stage 4	2 (18.2)	6 (3.2)	
OLGIM staging			0.2285 (chi-square - test for trend)
Stage 0	2 (18.2)	32 (16.9)	
Stage 1	3 (27.3)	62 (32.8)	
Stage 2	3 (27.3)	86 (45.5)	
Stage 3	2 (18.2)	6 (3.2)	0.0163
Stage 4	1 (9.1)	3 (1.6)	

Abbreviations: OLGA = Operative link for gastritis assessment; OLGIM = Operative link for intestinal metaplasia assessment.

Stratifying patients per successful treatment of *H. pylori* infection, no difference between groups was observed: in the group of not-cured patients, two patients developed gastric dysplasia and none developed gastric cancer (data not shown).

Patients who developed gastric carcinoids at follow up were characterized by the presence of pernicious anemia which was present in all of them compared to 50.6% of those without carcinoids ($p < 0.01$) and the absence of antral and/or corporal *H. pylori* at histology compared to 12.4% in those without carcinoids, albeit not statistically significant ($p = 0.4670$). Other features as age <50 years (60% vs. 38.6%), female gender (70% vs. 67%), co-presence of autoimmune diseases (80% vs. 50.6%), positivity to anti-parietal cell antibodies (100% vs. 72%) or gastrin values 12-fold over normal values (80% vs. 52.3%) were similar in the two groups.

In regard to gastric cancer and gastric carcinoids, the mean overall survival time (95% CI for the mean) free of lesions was 22.7 (21.9–23.4) years and 21.6 (20.5–22.8) years, respectively. Kaplan curves are shown in Figure 2.

Retrospective post-hoc analysis based on operative link for gastritis assessment and operative link for intestinal metaplasia staging system

Based on operative link for gastritis assessment (OLGA) and operative link for intestinal metaplasia (OLGIM) staging system, we performed a retrospective *post-hoc* analysis in order to understand whether patients who developed gastric cancer or dysplasia at follow up had higher OLGA or OLGIM stages compared to those who remained free of lesions during follow up.

In regard to OLGA, stages 1, 2, 3, and 4 were present at baseline in 19.5%, 67.5%, 9%, and 4% of patients, respectively. In regard to OLGIM, stages 0, 1, 2, 3, and 4 were present at baseline in 17%, 32.5%, 44.5%, 4%, and 2%, respectively. As shown in Table IV, gastric epithelial neoplastic lesions occurred at follow up more frequently in patients who had stages 3 and 4 by OLGA and OLGIM staging at baseline ($p < 0.05$). Analyzing OLGA and OLGIM staging in the four patients who developed gastric cancer at follow up, we observed that three had stage 2 and one had stage 4 by OLGA, whereas one had stage 0, one had stage 1, one had stage 2, and one had stage 4 by OLGIM.

Discussion

This prospective long-term follow-up study from 4 years upwards to more than 20 years showed an annual incidence rate person-year of 0.25% for gastric cancer in AG patients. Previously we reported a similar annual incidence rate person-year of 0.2% for gastric cancer at a median follow up of 4.3 years in 300 AG patients [7]. Another study detected, by yearly endoscopy over 10 years, 14 (8.4%) gastric cancers in 166 patients with dysplasia, intestinal metaplasia, AG, and in AG and intestinal metaplasia the risk of malignancy was 11% [5]. According to Globocan 2012, the annual incidence rate for gastric cancer in the general Italian population is estimated to be 0.004% [38]. This study, thus, confirms the increased risk of gastric cancer in AG.

The findings of this study further showed an annual incidence rate person-year of 0.7% for type I gastric carcinoids. This figure was nearly twofold compared to a previous study, in which an annual incidence rate person-year of 0.4% for these tumors was reported at a median follow up of 6.3 years [23]. Previous data on type I gastric carcinoids incidence focused on pernicious anemia patients only and are therefore not directly comparable to our findings. A 1998 study described eight new cases of type I gastric carcinoids in 416 patient-years corresponding to an annual incidence rate of 2% [21]. From a 1988 study, after 1397 patient-years, an annual incidence rate of 0.1% of type I gastric carcinoids can be calculated [22]. This higher incidence rate of type I gastric carcinoids might be due to the longer follow-up period which was increased up to a median of 7.5 years. However, the incidence of type I gastric carcinoids has been on the rise for over the past 30 years, as have all that of other neuroendocrine tumors. This may be the consequence of a true increase of tumor incidence, but it may also reflect an increased detection of these tumors due to more advanced diagnostic methods [39].

This study showed that in AG patients, at long-term follow up, the annual incidence rate person-year for all gastric neoplastic lesions taken together can be calculated to be as high as 1.36%. Formerly only patients with pernicious anemia have been investigated at varying follow-up periods [21,22,24–26]. Considering that the estimated burden of AG in the general population is up to 30%, according to a recent systematic review [40], a substantial number of persons may be at higher risk of gastric neoplastic lesions. Applying the prognostic staging systems OLGA and OLGIM, from this study, a significant higher frequency of stages 3 and 4 among patients with gastric cancer and dysplasia compared to those without ($p < 0.001$) emerged, suggesting the utility of this staging system with the limits of the retrospective *post-hoc* analysis.

From this study, another new result emerged: the incidence rates of gastric cancer and type I gastric carcinoids were not different ($p = 0.07$), indicating that AG patients are similarly exposed to both risks. The finding that, over time, two female patients developed first type I gastric carcinoids and subsequently at long-term follow-up gastric cancer further support the exposition to the double risk of gastric neoplastic lesions in AG. This risk is present in AG due to the pathophysiological changes related to gastric body atrophy, such as increased pH, reduced ascorbic acid, and scavenging of nitrites and other potential carcinogenic substances [41]. In recent years, it became apparent that besides *H. pylori*, other bacteria may be involved in gastric carcinogenesis; it has been shown that the gastric cancer microbiota was dominated by species of the genera *Streptococcus*, *Lactobacillus*, *Veillonella*, and *Prevotella*; albeit, the roles of these species in the development of gastric cancer needs to be determined [42]. Hypergastrinemia due to atrophy of oxyntic mucosa in AG is well known as a major pathogenetic factor for type I gastric carcinoids, because gastrin acts as a growth factor for enterochromaffin-like cells [17–19]. Hypergastrinemia has been proposed in many animal models of gastric carcinogenesis; in all species where long-term hypergastrinemia has been induced, an increased risk of gastric malignancy, with adenocarcinoma phenotype and even the signet-ring cells phenotype, was observed [43,44].

This study further showed that the patients' features associated with gastric cancer and type I gastric carcinoids were different, keeping in step with the different pathogenetic mechanisms of these two type of tumors [3,10–12,17–19]. The occurrence of type I gastric carcinoids and the survival free of gastric carcinoids was strongly linked to pernicious anemia, present in all

cases who developed this neuroendocrine neoplasia. Also, gastric autoantibodies were present in all patients with type I gastric carcinoids. These results suggest that type I gastric carcinoids are mainly associated with features of autoimmune gastritis. Gastric cancer, instead, was associated with the presence of *H. pylori* in the corporal mucosa (HR = 8). This finding keeps in step with the concept of corpus-predominant gastritis supporting the observations of Uemura et al. of more than 10 years ago that gastric cancer develops in *H. pylori*-positive patients and in those with severe gastric atrophy, corpus-predominant gastritis or intestinal metaplasia are at increased risk [10].

In our study the regular follow-up investigations permitted to successfully treat all patients with type I gastric carcinoids and two out of four gastric cancers. The fatal outcome of one gastric cancer patient was mainly related to his comorbidities rather than to the stage at which gastric cancer was diagnosed. In regard to type I gastric carcinoids, all lesions had benign behavior and could be endoscopically treated, avoiding gastric surgery in all cases. These findings raise the question of the benefit of regular endoscopic monitoring with standard bioptic mapping of antral and corporal mucosa in these patients in order to detect and properly treat type I gastric carcinoids, gastric dysplasia or cancer.

The present study has some strengths, as the prospective inclusion of patients with standardized diagnostic criteria for AG, the follow-up protocol, and long-term cohort study, but we are aware of some limits, as the long inclusion period, the relative small sample size, and the possible lack of generalizability of our results due to epidemiological differences in populations (i.e. East–West), in particular with regard to gastric cancer [45]. Another weakness is the relative high rate of lost at follow up which might have led to an underestimation of incidence rates of gastric cancer and carcinoids in this long-term follow-up cohort.

In conclusion, this study shows an annual incidence rate of 1.36% person-year for gastric neoplastic lesions in AG patients at long-term follow up. AG patients are similarly exposed to gastric cancer and type I gastric carcinoids.

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