Development of Type I Gastric Carcinoid in patients with Chronic atrophic gastritis

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DEVELOPMENT OF TYPE I GASTRIC CARCINOID IN PATIENTS WITH CHRONIC ATROPHIC GASTRITIS

Running Head : Type I Gastric Carcinoids in atrophic gastritis

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ABSTRACT

Background: Long-term observational studies assessing the incidence of Type I Gastric Carcinoid (GC) in patients with chronic atrophic gastritis are **few**. The aim of the present study was to evaluate the occurrence at diagnosis and during follow-up and to identify patient features associated with the presence of TypeIGC in a cohort of chronic atrophic gastritis patients.

Methods: 367 chronic atrophic gastritis patients (245 females, age 54[18-79]years) underwent regular follow-up by gastroscopy. The incidence of TypeIGC was determined in chronic atrophic gastritis patients with at least 2 years of follow-up (n=214). Baseline clinical and histological features were analysed as **factors associated** with the presence of TypeIGC by **univariate analysis**.

Results: TypeIGC was diagnosed in **9(2.4%)** patients at the moment when chronic atrophic gastritis was diagnosed. After 1463 person-years, 6 patients developed TypeIGC with an annual incidence rate (person-year) of 0.4 %. Patients with TypeIGC had significantly higher levels of gastrin, chromogranin A and more frequently the presence of body polyps and ECL-dysplasia **compared** with chronic atrophic gastritis patients without TypeIGC.

Conclusion: This cohort study shows that TypeIGC is a rare complication in patients with chronic atrophic gastritis and the presence of body polyps and ECL-dysplasia at gastroscopic/histologic evaluation are strongly associated with the presence of TypeIGC.

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INTRODUCTION

Gastric carcinoids (GC) or gastric neuroendocrine tumors are tumors derived from enteterochromaffin-like (ECL) cells which are localized in the gastric fundus and corpus. The main role of ECL-cells is the secretion of histamine that, in turn, stimulates acid secretion by parietal cells (1). GC were classified in three subgroups, Type I to Type III, with different pathogenic causes and outcomes (2-4). Type I lesions are more frequent, up to 80% of the total, and are gastrin-dependent tumors which are associated with atrophic gastritis (5). Gastrin, released by G-cells in the gastric antrum, is the main factor that regulates the release of histamine and produces trophic effects upon ECL-cells (6). In chronic atrophic gastritis (CAG), the loss of appropriate glands in the body leads to achlorhydria, and consequently, hypergastrinaemia. The chronic elevation of gastrin stimulates ECL- hyperplasia and sometimes the development of Type I GC (7-8). Given that only a small group of CAG patients develop Type I GC, factors other than gastrin are necessary for the progression of ECL-cells to Type I GC.

Recently, several large studies in different countries have reported an increasing incidence of all gastric neuroendocrine tumors (9, 10). Although older studies reported a prevalence rate of Type I GC between 1 to 12.5% in patients with CAG (11-13), an estimate of Type I GC incidence in patients with this specific condition is unknown. In fact, long-term observational studies assessing the incidence of Type I GC in CAG patients are few (13-15). For this reason, the aim of the present study was to evaluate the occurrence of Type I GC at diagnosis and during follow-up and to identify patient features associated with the presence of Type I GC in a cohort of CAG patients.

METHODS

Patients and Study Design

Between 1992 and 2008, we diagnosed the presence of CAG in 367 (245 females, median age 54 years, range 18-79 years) patients referred to our Unit for unexplained anaemia or long-standing dyspepsia, as described in detail elsewhere (16). Patients underwent gastroscopy with biopsies and those with proven histological diagnosis of CAG were informed about the increased risk of gastric neoplasia associated with CAG and about the need for regular follow-up by gastroscopy. Personal and clinical data, family history for gastric neoplasia and smoking habit were recorded for all patients during a clinical interview. Of the initial population, 102 patients dropped-out because 4 patients died from causes not-related to CAG and 98 patients refused to participate in further follow-up. Thus the study population included 265 patients (177 females, median age 54 years, range 20-79 years) (see Figure 1). The incidence of Type I GC was determined in CAG patients with at least 2 years of follow-up (n=214; median follow-up 6.3 [2-17]years), after the exclusion of prevalent Type I GC, because this interval of time was considered sufficient for the development of a new lesion of Type I GC. Regarding demographic (gender and age) and clinical features (severity of atrophy), there were no significant differences between patients of the initial CAG group (n=367), of the baseline population (n=265) and of follow-up population. Diagnosis of CAG was based on the presence of fasting gastrin above upper normal values and the histological confirmation of gastric body (corpus and fundus) atrophy based on 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 body along the greater curve (16-17). The degree of gastritis was assessed according to the updated Sydney System (18). Atrophy of the gastric body mucosa was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands. Atrophy of the antral mucosa was defined as focal or

1
2 complete disappearance of antral glands or their replacement by intestinal metaplastic epithelium
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4 (16).
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6 The ECL-cell status was assessed according to the Solcia classification (19). Hyperplasia was
7
8 defined by ECL cells proliferation < 150 µm and classified as: normal pattern, simple, linear,
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10 micronodular and adenomatoid. The diagnosis of dysplasia was based on ECL proliferation
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12 between 150 and 500 µm, while that of carcinoid on ECL proliferation >500 µm. MEN-I
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14 diagnosis was excluded (20-21). In case of a visible lesion, additional biopsies were obtained.
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17 All biopsies were examined independently by two experienced pathologists (CB, EP), unaware
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19 of the clinical data of the patients. In the event of disagreement, the biopsies were re-examined
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21 simultaneously by both pathologists until agreement was reached (16).
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24 Pernicious anaemia was defined as low hemoglobin concentration, MCV>100 fl together with
25
26 low B12 vitamin levels, responding to intramuscular B12 vitamin treatment (22). Iron
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28 deficiency anaemia was defined as low hemoglobin concentration, MCV<80 fl and ferritin<30
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30 ng/ml (22). The diagnosis of autoimmune thyroid disease (AITD) was based on the presence of
31
32 thyroid autoantibodies and thyroiditis signs at ultrasound evaluation irrespective of thyroid
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34 function as previously described (23).
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37 Plasma gastrin levels were determined by radioimmunoassay using antiserum 4562, kindly
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39 supplied by Prof. J.F. Rehfeld, Copenhagen, Denmark, as previously described (gastrin normal
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41 values ≤40 pg/ml) (13). Chromogranin A (CgA) levels was assessed by ELISA kit (Dako A/S,
42
43 Glostrup, Denmark) (CgA normal values ≤ 98 ng/ml); Pepsinogen I was measured using a
44
45 commercial RIA kit (Pepsik; Sorin, Saluggia, Italy; normal values 20-80 ng/ml); Parietal cell
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47 antibodies (PCA) were measured by immunofluorescence and *H pylori* IgG antibodies using an
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49 ELISA commercial kit (GAP test IgG, Biorad, Milan, Italy) (16). *H pylori* infection was
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51 considered positive when the bacterium (Giemsa stain) was detected at histology and/or on the
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53 basis of a positive IgG titre for *H pylori* (17). Bismuth-based triple regimen eradication therapy
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55 was prescribed in the case of *H pylori* positivity and, after 6 months, the absence of *H pylori* at
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histology and a decrease by at least 50% in the initial titre of *H pylori* IgG was the criterion for the successful cure of infection (17).

Follow-up Protocol

The first follow-up gastroscopy was scheduled at intervals between 2 and 4 years after diagnosis of CAG and the same baseline bioptic sampling was repeated (24).

If Type I GC was detected, an extensive bioptic sampling of at least ten biopsies (2 biopsies in antrum, 4 in gastric body and 4 in the fundus) of the gastric mucosa was taken after 6 and 12 months (13). If Type I GC was not confirmed at two following gastroscopies, patients were followed by the general follow-up protocol. Polypoid lesions up to 5 mm were removed by forceps, otherwise an electrocautery snare was used. All patients with a diagnosis of Type I GC underwent at least one imaging procedure for the tumor staging (Octreoscan, CT-scan, Magnetic Resonance Imaging).

Data Analysis and Statistical Evaluation

Type I GC at diagnosis and during follow-up in CAG patients was evaluated and prevalence and incidence rates (person-year) were calculated. Quantitative data are presented as medians and ranges or, absolute counts and percentages. Mann-Whitney and Fisher exact test were used when appropriate.

Univariate analysis was performed to identify patient features associated with the presence of Type I GC. The following baseline patient characteristics were analysed: age at CAG diagnosis, gender, presence of atrophic pangastritis defined as the concomitant presence of atrophy in the gastric antrum and body, presence of pernicious anaemia, gastrin, pepsinogen I, CgA, presence of PCA, presence of dyspepsia, presence of gastric polyp, presence of ECL-dysplasia, smoking habits, presence of *H.pylori*, family history for gastric cancer and presence of AITD. A p value of less than 0.05 was considered statistically significant.

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RESULTS

Occurrence of Type I GC

Type I GC were diagnosed in 9 out of 367 (2.4%) patients at the moment of the initial diagnosis of CAG (6 female, median age 59 [range 40-72] years). As shown in **Table 1**, all Type I GC patients but one presented polyps of the body with a diameter between 0.3 and 3 cm at gastroscopy. In 6 out of 9 (66.7%) patients with Type I GC, the body gastric mucosa presented a severe atrophy, in the remaining cases the atrophy was moderate. The alterations of ECL-pattern associated with Type I GC were micronodular hyperplasia (n=4; 44.5%) and dysplasia (n=5; 55.5%). Further details of CAG patients with Type I GC such as the presence of pernicious anemia, the levels of gastrin and CgA, the degree of body atrophy are summarized in the **Table1**.

Of the initial population, after the exclusion of 102 patients who dropped-out, 265 patients remained in the study and of these, 214 patients had at least 2-years follow-up (see Figure1). After 1463 person-years, 6 patients developed Type I GC with an annual incidence rate (person-year) of 0.4 % (3 female, median age 57 [range 23-69] years) (Table 1). Two out of 6 patients with incident Type I GC presented ECL dysplastic lesions at first diagnosis of CAG. Observed ECL-pattern alterations associated with Type I GC were linear (n=1; 16.7%), micronodular (n=2; 33.3%), adenomatoid (n=1; 16.7%) hyperplasia and dysplasia (n=2; 33.3%).

Patient Features associated with Type I GC

To identify patient features associated with the presence of Type I GC, we compared baseline clinical, biochemical and histological characteristics between CAG patients without (n=199) and with Type I GC (n=15). As shown in **Table 2**, patients with Type I GC presented significantly higher levels of gastrin and CgA with respect to the other group. At the moment of the diagnosis of Type I GC, 7 out of 15 Type I GC patients (46.6%) had a diagnosis of ECL-dysplasia with

respect to none of the other group ($p < 0.000001$). Other analyzed features were similar between the two groups.

Regarding the features of gastric polyps, the gastric location, the numbers and the endoscopic appearance (sessile or pedunculated) of the polyps were not significantly different between CAG patients with and without Type I GC (see **Table 3**). Body polyps were more frequently found in patients with Type I GC with respect to the other group ($p = 0.000001$). Twelve out of 15 (80%) polyps diagnosed in CAG patients without Type I GC were hyperplastic while the remaining were adenomas (3/15, 20%).

Management and Follow-up of Type I GC

All polypoid lesions up to 12 mm underwent endoscopic polypectomy. Endoscopic polypectomy failed on the polyp of 3 cm because of its hard consistency. The patient, a man aged 55, underwent total gastrectomy. At histological evaluation, the tumor extended from the mucosa to the submucosa and infiltrated the muscularis propria. Immunohistochemistry showed positivity for CgA and VMAT-2 with Ki67 proliferation index lower of 1%. In three out of 19 local lymph nodes removed during the surgery a metastatic endocrine tumor was found. When Type I GC was diagnosed, CT-scan and Octreoscan were performed and resulted negative.

In 6 out of 15 (40%) patients with Type I GC, there was a recurrence of the tumor, but all lesions were small (up to 1 cm) and underwent endoscopic polypectomy (see **Table 1**). At the end of the study, all the patients were alive and in good health.

Concomitant GI Findings

During an overall median follow-up of 6.3 [2-17] years, three intestinal-type adenocarcinomas were diagnosed [2 female; median age 51 (51-77) years]. All three were located in the gastric antrum and were diagnosed 8, 5 and 1 years after diagnosis of CAG. The stage of the gastric cancer was T2N1M0 in the male patient, and T1N0M0 in the two female patients. After

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gastrectomy, two patients died, one for neoplastic disease progression and the other for complications after surgery. At the end of the study, one female patient was alive and free of neoplasia.

DISCUSSION

In the present work, we followed-up a cohort of CAG patients for 1463 person-years and found an annual incidence rate (person-year) for the Type I GC of 0.4%. Recently, large studies on population-based data in different countries have reported an increasing incidence of GC among all gastric malignancies and an increase of these among all gastrointestinal carcinoid lesions (9-10). This increase could be partially explained by the increased diffusion of diagnostic gastroscopy (25) and correlates temporally with the increasing use of proton pump inhibitors (26). To our knowledge, few studies evaluated the real incidence of Type I GC in patients with CAG because the surveillance of CAG was not recommended (27). An old study by Kokkola et al described 8 new cases of Type I GC in 416 patient-years which corresponds to an annual incidence of 2% (14). Sjoblom et al studied 196 patients with pernicious anemia, but gastroscopy was performed only in 70 of these patients (15). After 1397 patient-years, 2 new cases of Type I GC were reported on hospital registries among the initial group of 196 patients. This figure should correspond to an annual incidence rate of 0.1%, but in this study not all patients underwent gastroscopy and the incidence rate can only be obtained indirectly. These differences in the Type I GC incidence rates could be explained by the patient selection. CAG can have a wide range of clinical presentations as already reported (28). Patients included in our series had dyspepsia, iron deficiency anemia or pernicious anemia. In particular, the latter was present in almost 50% of our patients, while previous studies included exclusively patients with pernicious anemia. In our previous study, we diagnosed 1 new case of Type I GC in a smaller sample of CAG patients (n=96) for a shorter period of observation (median time of 2.5 years) which corresponds to an annual incidence of 0.4% (13). Thus, in the present study, increasing both the

cohort of CAG patients and follow-up period (median time of 6,3 years) the annual incidence rate remained constant.

At initial diagnosis of CAG, we observed 9 cases of Type I GC which is 2.4% of all patients.

Previous studies reported a rate between 1% and 12.5% of Type I GC (11,13- 15,29-30). The wide range of the prevalence rates of Type I GC among several studies could be explained by different settings where patients were selected, such as type of hospital (secondary, tertiary center), symptoms/signs of presentation, type of patient (in-patient, out-patient).

In order to identify patient features associated with the presence of Type I GC, we compared the baseline features between CAG patients with and without Type I GC. Higher levels of gastrin and CgA were associated with the presence of Type I GC by univariate analysis. A recent review has confirmed that the CgA is the most sensitive biomarker in neuroendocrine tumors and it is more frequently elevated in well-differentiated tumors compared to poorly differentiated ones (31). However, patients with atrophic gastritis present high values of CgA (32) and the low specificity of the CgA assay does not identify those with Type I GC among CAG patients as already reported (33). For the same reasons, gastrin does not detect patients with Type I GC as it is increased in all CAG patients. In fact, as shown in Table 2, although patients Type I GC had a median value of gastrin higher than the other CAG patients, the ranges of gastrin overlapped widely between the two groups. We retain that these assays are clinically useful for identifying patients with CAG diagnosis or to exclude those from patients with Type III GC, but they cannot be considered as markers of the presence of Type I GC.

The presence of ECL-dysplasia was associated more frequently with Type I GC. This pattern of ECL-cells is considered to be the true gastric carcinoid precursor lesion and it can represent the sign of a concomitant carcinoid lesion (19). Our previous study showed that this lesion also carries an increased risk for the development of Type I GC during the follow-up (13). Thus, CAG patients with a diagnosis of ECL-cell dysplasia could benefit from a shorter endoscopic

1 follow-up to exclude concomitant Type I GC lesions or to identify new lesions in the gastric
2 mucosa.
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6 Another finding of the present study was that the presence of body polyps increases the risk of a
7 Type I GC in CAG patients. Unfortunately, no features of endoscopic appearance of the gastric
8 polyps (size, number, sessile/penduculated presentation) permitted a differential diagnosis
9 between patients with and without Type I GC. In the group of CAG patients without Type I GC,
10 almost three-fourth of all polyps were hyperplastic and the remaining were adenomas.
11 Hyperplastic polyps are very common among all benign epithelial gastric polyps (42,43) and
12 more frequently associated with CAG (44,45). Importantly, some authors have reported an
13 increased risk of neoplastic progression also for this type of lesions. Moreover, CAG has an
14 increased risk of gastric adenocarcinoma (14,15). As a consequence, each polyp found at
15 gastroscopy should be removed and histologically examined.
16
17 Different approaches were proposed for the management of Type I GC such as surgery (34),
18 endoscopic polypectomy (1,4,12), somatostatin analogs (35,36) and an endoscopic follow-up
19 without any specific treatment (37,38). We used a conservative management by endoscopic
20 follow-up and performing polipectomy of all visible polypoid lesions. Only one patient, in
21 which the endoscopic approach failed, underwent gastrectomy. This patient had a deeper
22 neoplastic lesion in the gastric wall, extended to muscularis propria and metastatic involvement
23 of three lymph nodes. Thus, the surgery in this particular case was appropriate. After surgery,
24 imaging procedures (CT-scan and Octreoscan) for the staging did not reveal metastatic
25 involvement of the other organs. The possibility of more invasive lesions among Type I GC is
26 already described in the literature (39,40) and for patients with larger polyps, local surgical
27 tumor resection is recommended (41).
28
29 Finally, in our study, the rate of recurrence of the Type I GC during follow-up was almost of
30 40%. This high recurrence rate could be explained by Type I GC misdiagnosis during the
31 previous gastroscopy, by bioptic sampling errors or the continuous trophic effect of

hypergastrinemia on the gastric mucosa. Endoscopic follow-up every 6-12 months, as suggested also by ENETS guidelines, allowed us to identify recurrent lesions or new lesions (incidence-cases) when they had a small size and were easily removable by polypectomy without complications (46). This approach was safe, and the 100% survival of all Type I GC within the study period is in keeping with previous works (37,40).

Our study has some limitations. The first is the high number of CAG patients who dropped-out during the follow-up, almost 27%. We do not know the clinical outcomes of these CAG patients and, as a consequence, the incidence rate could be underestimated. However, we know that this group of patients did not present demographic or baseline clinical features different from the CAG patients who remained in the study and we retain that the main findings of this study remain generally valid.

Moreover, the power of the statistical analysis was limited by the small numbers of case-findings of Type I GC. However, larger number of case-findings could be obtained only performing studies with larger cohorts and longer period of observation.

In conclusion, this cohort study implies that Type I GC is a rare complication in patients with CAG and the presence of body polyps at gastroscopy and ECL-dysplasia at histological evaluation are strongly associated with the presence of Type I GC.

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Conflict of Interest: None

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LEGEND TO FIGURES

Figure 1: Study population

Figure 2: Kaplan-Meier Analysis: Intervals between initial diagnosis of atrophic body gastritis and diagnosis of Type I gastric carcinoids. Proportion of patients with atrophic body gastritis who remained free of Type I gastric carcinoids.

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For Peer Review

TABLE 1: Baseline features of 15 CAG patients with prevalent and incident Type I GCs.

Patients	Gender	Age (years)	Gastrin (pg/ml)	CgA (ng/ml)	Body Atrophy *	Pernicious Anaemia	Endoscopic Findings	Detection of Type I GC	Recurrence
1	F	45	305	60	2	No	Body polyp of 0.5 cm	At Diagnosis	No
2	M	67	975	175	3	Yes	Body polyp of 0.5 cm	At Diagnosis	At 4-month follow-up
3	F	40	975	150	3	No	Body polyp of 0.6 cm	At Diagnosis	No
4	F	40	570	140	3	No	Normal mucosa	At Diagnosis	At 6,15,32-month follow-up
5	F	66	690	245	3	No	Body polyp of 0.5 cm	At Diagnosis	No
6	F	72	680	250	3	Yes	Body polyp of 0.5 cm	At Diagnosis	At 3,5-month follow-up
7	M	59	2000	167	2	Yes	Body polyp of 0.3 cm	At Diagnosis	No
8	F	61	1150	150	3	Yes	Body polyp of 0.5 cm	At Diagnosis	No
9	M	55	1183	547	2	No	Body polyp of 3 cm	At Diagnosis	No metastasis after total gastrectomy
10	M	47	1090	150	3	Yes	Normal mucosa	At 31-month follow-up	At 35,46,64-month follow-up
11	M	67	500	405	2	No	Body polyp of 0.5 cm	At 31-month follow-up	No
12	M	69	220	120	3	No	Body polyp of 0.5 cm	At 41-month follow-up	No
13	F	65	2800	370	3	No	Normal mucosa	At 7-month	At 13,18,50-month

								follow-up	follow-up
14	F	23	565	230	3	Yes	Body polyp of 1.2 cm	At 59-month follow-up	No
15	F	49	1475	240	3	Yes	Body polyp of 0.4 cm	At 18-month follow-up	At 30,37,61-month follow-up

* scored accordingly to the Sydney System.

TABLE 2: Baseline clinical, biochemical and histological features of 214 CAG patients with and without Type I GC.

	Type I GC n=15	CAG n=199	<i>p</i>
Age, years (range)	59 (23-72)	54 (22-77)	0.39
Female gender, n (%)	9 (60)	137 (68.8)	0.7
Gastrin, pg/ml, median (range)	832.5 (220-2800)	500 (50-2700)	0.01
Pepsinogen I, ng/ml, median (range)	10 (3-28)	10 (3-79)	0.6
Chromogranin A, ng/ml, median (range)	171 (60-405)	100(30-280)	0.0001
Pernicious Anemia, n(%)	7 (46.6)	98 (49.2)	1
Family history for gastric cancer, n(%)	3 (20)	18 (9)	0.13
Smoking habit, n(%)	8 (53.3)	81 (40.7)	0.39
PCA, n(%)	14(93.3)	158(79.3)	0.3
<i>Hp</i>ylori positivity , n(%)	7 (46.6)	84 (42.2)	0.79
Dyspepsia, n(%)	7(46.6)	43 (21.6)	0.05
AITD, n(%)	9(60)	91(46)	0.29
ECL-dysplasia*, n(%)	7 (46.6)	0	<0.000001
Atrophic pangastritis, n(%)	2(13.3)	44(22.1)	0.5
Body Atrophy, n (%)	0	22(11.3)	0.37
Mild	4(26.6)	55(27.4)	1
Moderate	11(73.4)	122(61.3)	0.4
Severe			

PCA=parietal cell antibodies; CAG= chronic atrophic gastritis; AITD=autoimmune thyroid disease

***ECL-dysplasia was concurrent at Type I GC in 5 prevalent and 2 incident cases.**

Data are expressed as median(range). Mann-Whitney test or Fisher-test were used for the comparison of baseline features between two groups

TABLE 3: Comparison of gastric polyps in CAG patients with and without Type I GC.

POLYPOID LESION	Type I GC§ n=15*	CAG# n=199	<i>p</i>
Gastric Location			
Antrum	0	6(3)	ns
Body	12(80)	7(3.5)	0.000001*
Antrum and Body	0	2(1)	ns
Size			
<0.5 cm	9/12(75)	7/15(46.7)	ns
0.5-1 cm	2/12(16.7)	6/15(40)	ns
>1 cm	1/12(8.3)	2/15(13.3)	ns
Numbers			
Single	5/12(41.6)	8/15(53.3)	ns
Multiple	7/12(58.3)	7/15(46.7)	ns
Endoscopic Appearance			
Sessile	12/12(100)	12/15(80)	ns
Pedunculated	0	3/15(20)	ns

§ reported polypoid lesions refer to gastroscopy performed at the moment of type I GC diagnosis; # reported polypoid lesions refer to baseline gastroscopy; *3patients had intramucosal carcinoids;
Data are expressed as proportions and Fisher-test was used for the comparison between the two groups.

***n*=367** patients with atrophic body gastritis referred to the Department of Digestive and Liver Diseases between January 1992 and June 2008

Excluded Patient from the study because:

- *n*=4 died for other causes
- *n*=98 lost at follow-up

***n*=265** baseline population

Excluded Patients from the incidence calculation:

- *n*=51 follow-up < 2 years

***n*=214 (80.7%)** follow-up population

120x147mm (400 x 400 DPI)