

Type I Gastric Carcinoids: A Prospective Study on Endoscopic Management and Recurrence Rate

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Key Words

Gastric carcinoid · Atrophic gastritis · Recurrence · Follow-up · Endoscopic management

Abstract

Background: Type I gastric carcinoids (TIGCs) are neuroendocrine neoplasms arising from enterochromaffin-like cells in atrophic body gastritis. Data regarding their evolution in prospective series are scarce, thus treatment and follow-up are not codified. Our aim was to evaluate clinical outcome and recurrence in TIGCs managed by endoscopic approach.

Methods: 33 patients (24 females; median age 65 years, range 23–81) were included and managed through endoscopic follow-up every 6–12 months, with lesion removal and multiple gastric biopsies. Baseline clinical and histological features were analyzed as risk factors by Cox regression.

Results: At diagnosis, 7 tumors were intramucosal carcinoids and 26 were polyps (median diameter 5 mm, range 2–20), multiple in 17 patients. Associated severe atrophy was present in 21 cases (63.6%), while mild atrophy was found in 6 cases (18.2%). During a 46-month median follow-up, survival was 100% and no metastases occurred. One patient developed a less-differentiated carcinoid that was radically treated by surgery. 21 patients (63.6%) had recurrence after a me-

dian of 8 months, 14 of these (66.6%) had a second recurrence after a median of 8 months following the previous carcinoid removal. Median recurrence-free survival was 24 months. Neither clinical nor biochemical recurrence-predicting factors were found. **Conclusions:** Although about 60% of TIGCs had recurrence after endoscopic resection, endoscopic management may be considered safe and effective.

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Introduction

Gastric carcinoids (GCs) are classified into three categories: type I, arising on atrophic body gastritis (ABG); type II, a manifestation of type I multiple endocrine neoplasia (MEN-I); type III, with no specific background disease [1].

The incidence of this type of tumor has been rising over the last 30 years, as have all other neuroendocrine tumors (NETs) [1–3]. Type I gastric carcinoids (TIGCs) are 75% of all GCs and occur in 1–2% of ABG patients from enterochromaffin-like (ECL) cells which, since ABG-induced hypergastrinemia stimulates their growth, may undergo a multistep process from ECL hyperplasia through dysplasia to neoplasia [1–2, 4–9].

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Often TIGCs do not show any ABG-related specific signs/symptoms (dyspepsia, anaemia), and diagnosis follows an accidental finding during esophagogastroduodenoscopy (EGD) [1, 10]. They are well-differentiated NETs with low Ki67 index, often multiple, usually of gastric fundus/body. These tumors are frequently represented by macroscopic lesions (polyps) of small diameter (<2 cm), but 25% of TIGC are not macroscopically visible during EGD and can only be detected at histological examination; in these cases, they are called 'intramucosal carcinoids' [1].

Previous studies on TIGCs were retrospective and either based on small case series or analysis of all GC types together. Although most of them showed an indolent behavior of this disease, few cases of regional or distant invasion (liver/lymph node metastases) were described [2, 5, 9, 11–19].

TIGC management has not yet been codified, and several approaches have been suggested. Gastric surgery has been proposed for multiple or large lesions, or for patients with recurrence after endoscopic resection, in order to definitively stop hypergastrinemia by antrectomy, or radically remove TIGC by total gastrectomy [9, 20–22]. Somatostatin analogs (SAs) have also been proposed as they decrease tumor growth both in vitro and in vivo [9, 23–27]. A further alternative evaluated is the conservative management by serial endoscopic controls and lesion removal; however, among the few studies evaluating this option, most of them are based on small sample sizes, include patients managed by different strategies and in addition to this, recurrence data are scanty [9, 11–13, 17, 22, 28–29]. Therefore, the aim of our study was to evaluate the clinical outcome (survival and malignant progression) as primary endpoint, and the recurrence rate and risk after endoscopic resection as secondary endpoint, in a consecutive series of prospectively enrolled TIGC patients all managed by endoscopic approach.

Methods

Patients and Study Design

All consecutive patients examined at our Unit from 1993 to 2008, having histological diagnosis of TIGC and at least one follow-up EGD, were prospectively enrolled. All patients gave their informed consent at entry, and the study was approved by the local ethical committee.

ABG diagnosis was based on hypergastrinemia and histological confirmation of gastric body atrophy on multiple biopsies performed in gastric antrum and body [30–34]. Gastritis was evaluated 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) [35]. Antral atrophy was defined as focal or complete disappearance of antral glands or their replacement by intestinal metaplastic epithelium [30].

In order to define ECL status, according to Solcia et al. [7], ECL cells proliferation with a diameter <150 μm was considered 'hyperplasia', distinguished in: normal pattern/simple hyperplasia, linear, micronodular and adenomatoid hyperplasia. Instead, dysplasia was diagnosed with a proliferation >150 but <500 μm , while if proliferation was >500 μm , it was defined as TIGC.

As previously reported, the diagnosis of pernicious anaemia was based on the presence of macrocytic anemia (hemoglobin <14 g/dl for men, <12 g/dl for women; mean corpuscular volume >100 fl), low vitamin B₁₂ (<197 pg/ml) responding to intramuscular vitamin B₁₂ treatment, and ABG diagnosis [36].

As already described, diagnosis of autoimmune thyroid disease (AITD) was based on the presence of thyroid autoantibodies and ultrasound compatible with thyroiditis, regardless of thyroid function [37].

Laboratory tests prescribed were: blood cells count, parietal cells antibodies (PCA), fasting serum gastrin (normal value <40 pg/ml), chromogranin A (CgA; normal value <98 ng/ml), ferritin (normal value >11 ng/ml), vitamin B₁₂ (normal value 211–1,132 pg/ml), IgG *Helicobacter pylori* (Hp) antibodies. Gastrin and CgA were measured by radioimmunoassay, PCA by immunofluorescence and Hp antibodies by ELISA commercial kit. If patients were taking PPI or H₂ blockers, treatment was stopped at least 2 weeks before performing the laboratory tests. Hp status was considered as 'positive' when a positive Hp immunoglobulin G titer was detected and/or bacteria were revealed at histology. Thus, bismuth-based triple regimens eradication therapy was prescribed and efficacy assessed by histology and serology after 6 months. MEN-I was also excluded by means of a questionnaire regarding symptoms, personal and family history, and through laboratory tests [34, 38].

Patients enrolled had a first endoscopic control 6 months after diagnosis; however, EGD was repeated if diagnosis had been made at a different hospital without multiple gastric biopsies, or if polypectomy had not been margin free. Subsequent follow-up was planned as follows: laboratory monitoring (blood cells count, ferritinemia, vitamin B₁₂) and visit every 6 months (to define follow-up program and prescribe support therapy in case of anemia, vitamin B₁₂ deficiency or dyspepsia); serial upper EGDs after 6 months from previous EGD in case of recurrence, after 12 months if not recurring.

EGDs were performed under sedation with 2001 GIF-Q20 Olympus optical endoscope and after 2001 with Olympus video gastroscope GIF-Q165. During EGD, all visible lesions were removed and multiple biopsies were taken from gastric body and antrum, as previously reported, using a standard oval fenestrated biopsy forceps (Olympus Optical Co., Ltd., Tokyo, Japan) [4].

Lesions were resected through forceps as 'cold biopsies' if diameter was up to 5 mm, otherwise an oval electrocautery snare was used after injection of normal saline + epinephrine solution (1:10,000). In the case of large lesions, since 2004 endoscopic ultrasound (EUS) was prescribed to assess wall invasion before resection; this procedure was performed after sedation by intravenous propofol, using a Pentax EG-3630UR endoscope.

Table 1. General features at diagnosis of the 33 TIGC patients enrolled

Patient features	Overall	Recurrence		p
		yes (n = 21)	no (n = 12)	
Gender, female	24 (72.7)	16 (76.2)	8 (66.6)	0.54
Median age (range), years ^a	65 (23–81)	65 (26–81)	63 (23–76)	0.69
Smoking, present and past	19 (57.6)	13 (61.9)	6 (50)	0.64
First-degree family history of gastric cancer	4 (12.1)	3 (14.3)	1 (8.3)	0.30
First-degree family history of peptic ulcer	7 (21.2)	4 (19.0)	3 (25)	0.53
Presence of autoimmune disease ^b	21 (63.6)	14 (66.6)	7 (58.3)	0.23
Dyspepsia	21 (63.6)	13 (61.9)	8 (66.6)	0.68
Anemia	25 (75.7)	18 (85.7)	7 (58.3)	0.06
IDA	15			
PA	10			
PCA positivity ^c	24 (86.2)	15 (88.2)	10 (83.3)	0.40
Median serum gastrin (25–75th IQR), pg/ml	570 (360.4–1,125)	652.5 (397.6–1,125.7)	550.3 (345.2–736.7)	0.99
Median serum CgA (25–75th IQR), ng/ml	208 (150–263)	241.5 (150–263)	178 (149.5–237.5)	0.74
<i>H. pylori</i> infection	11 (33.3)	8 (38.1)	3 (25)	0.82

^a For increase of one unit. ^b Autoimmune thyroiditis and/or type I diabetes mellitus. ^c Available in 29 patients. IDA = Iron deficiency anemia; PA = pernicious anemia; PCA = parietal cell antibodies; CgA = chromogranin A. Figures in parentheses are percentages unless otherwise indicated.

EGDs were performed by two expert endoscopists sharing diagnostic criteria and terminology, and the two expert pathologists who made the histological evaluation used the same terminology and diagnostic criteria.

A complete gastric map (2 biopsies in the antrum, 4 in the gastric body and 4 in the fundus) was performed at each follow-up EGD to describe gastritis score and potentially identify intramucosal carcinoids [4].

The specimens were formalin-fixed and routinely processed. 5- μ m-thick mucosal gastric sections were stained with hematoxylin-eosin for routine examination, Giemsa staining for Hp and Alcian blue-PAS staining for evaluation of intestinal metaplasia; monoclonal antibody anti-CgA (Clone DAK-A3; Dako, Glostrup, Denmark) by streptavidin-biotin kit (peroxidase detection system, Novocastra; Newcastle, UK) for immunostaining of endocrine cells was also used.

The total follow-up period was expressed as the time from diagnosis to the last EGD. Time to recurrence was defined as the time interval between endoscopic tumor resection and tumor recurrence found during follow-up.

EGD-related complications were recorded at diagnosis and during follow-up.

On admission, the following data were collected in an electronic database to be analyzed as risk factors for TIGC recurrence: sex, age, smoking (present and past), presence of dyspepsia, presence of anemia, first-degree family history of gastric cancer and peptic ulcer, presence of thyroiditis and type I mellitus diabetes, laboratory values, TIGC features, resection by forceps versus snare, grade of atrophy, ECL status, Hp infection.

Data Analysis and Statistical Evaluation

Statistical analysis was performed using a dedicated software (MedCalc[®] 9.6, www.medcalc.be). Data were expressed as median (range or 25–75th interquartile range, IQR). Analysis of recurrence-free survival (RFS) was performed by Kaplan-Meier method, univariate analysis for risk factors was done by Cox-proportional hazards regression model. p was statistically significant when <0.05.

Results

33 patients (M:F = 9/24), median age of 65 years with median gastrin rate of at least 10-fold higher than normal value, were included in this study (table 1).

At diagnosis 26/33 (78.8%) patients had polypoid tumors (median diameter 5 mm; range 2–20 mm), multiple in 17/26 (65.4%), and 7/33 (22.2%) had intramucosal carcinoids (table 2). In 54.5% of patients endoscopic removal was performed by forceps, in 45.5% by snare. All the cases were margin-free after lesion removal and did not need a short-term control to complete eradication. No procedure-related complications or need for hospitalization occurred.

21/33 (63.6%) patients had severe atrophy, 6 (18.2%) had moderate and 6 (18.2%) mild. 30.3% of patients had also antral atrophy, with a subsequent diagnosis of multifocal atrophic gastritis (MAG).

Table 2. Endoscopic and histological findings at diagnosis of the 33 TIGC patients enrolled, n (%)

Patient features	Overall	Recurrence		p
		yes (n = 21)	no (n = 12)	
<i>Endoscopic findings at diagnosis</i>				
Polyp	26 (78.8)	16 (76.2)	10 (83.4)	0.57
Multiple lesions	17 (65.4)	12 (57.1)	5 (41.6)	0.20
Median polyp diameter (range), mm	5 (2–20)	4 (2–10)	5 (3–12)	0.48
Resection by forceps	18 (54.5)	13 (61.9)	5 (41.6)	0.13
<i>Histological findings at diagnosis</i>				
Gastric body atrophy degree				
Severe	21 (63.6)	15 (71.4)	6 (50)	0.08
Moderate	6 (18.2)	2 (9.5)	4 (33.3)	0.20
Mild	6 (18.2)	4 (19)	2 (16.6)	0.42
MAG	10 (30.3)	8 (38.1)	2 (16.6)	0.43
ECL pattern				
Simple or linear hyperplasia	6 (18.2)	4 (19)	2 (16.6)	0.74
Micronodular hyperplasia	12 (36.4)	6 (28.5)	6 (50)	0.60
Adenomatoid hyperplasia	4 (12.1)	3 (14.3)	1 (8.4)	0.43
Dysplasia	11 (33.3)	8 (38.2)	3 (25)	0.33
Presence of intramucosal carcinoid	7 (21.2)	5 (23.8)	2 (16.6)	0.57

ECL alterations were observed in all patients: 66.7% hyperplasia (18.2% simple or linear, 36.4% micronodular, 12.1% adenomatoid), 33.3% dysplasia.

Median follow-up time was 46 months (range 4–123), with a median of 5 EGDs (2–13) per patient. No tumor-related death was recorded during observation.

In the 11 patients who underwent EUS, 8 TIGCs were limited to mucosa and 3 to submucosa, with no lymph node involvement observed in these patients. Moreover, during follow-up at least one imaging procedure was performed per patient (CT scan, magnetic resonance imaging, Octreoscan), with no evidence of either local or distant spread.

During follow-up, after initial resection, 21/33 (63.6%) patients had tumor recurrence but 12 had no subsequent TIGCs. Overall, median RFS was 24 months, and 1-year RFS was 53.8% (fig. 1). Median time to the first recurrence was 8 months (3–55 range). 20/21 (95.2%) recurring lesions were polyps, multiple in 11 cases (52.4%). 14/21 (66.6%) recurring patients had at least one subsequent recurrence, as shown in table 3.

One of these patients developed a 1.5-cm ulcerated sessile polyp in the gastric body as a fourth recurrence, which the histological report diagnosed as a poorly differentiated carcinoid with high proliferative index. EUS and CT scan described the lesion as limited to submucosa, and excluded the presence of metastases. The patient was

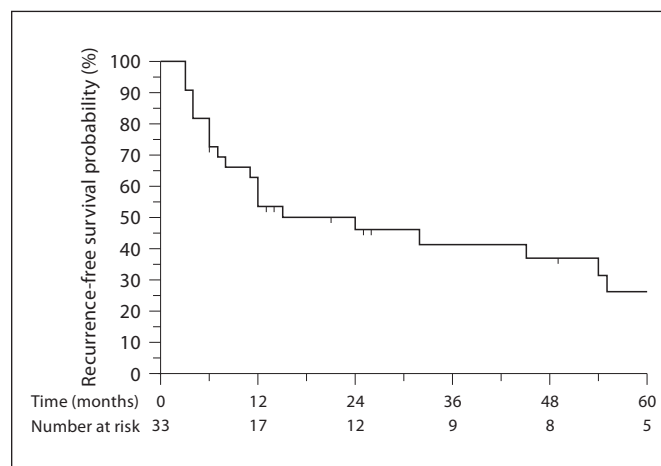


Fig. 1. TIGC recurrence-free survival during follow-up. 21/33 (63.6%) patients had tumor recurrence after endoscopic resection, with a median time to recurrence of 8 months (range 3–55).

treated by total gastrectomy with lymphadenectomy, and did not need any adjuvant therapy (pT2 N0 M0).

No risk factors for recurrence were identified at univariate analysis (table 1, 2). However, severe atrophy and anemia were both higher in recurring patients, although statistical significance was barely missed (85.7 vs. 58.3%, $p = 0.06$ and 71.4 vs. 50%, $p = 0.08$, respectively).

Table 3. Recurrence features in the 33 TIGC patients enrolled

Recurrence	Recurrent patients/total n (%)	Recurrence time median (range) months	Polypoid TIGC/total n (%)	Patients with multiple lesions/total n (%)
None	12/33 (36.4)			
1st	21/33 (63.6)	8 (3–55) ^a	20/21 (95.2)	11/21 (52.4)
2nd	14/21 (66.6)	8 (2–26) ^b	12/14 (85.7)	7/14 (50)
3rd	6/14 (42.8)	19 (4–32) ^b	6/6 (100)	3/6 (50)
4th	2/6 (33.3)	5.5 (4–7) ^b	2/2 (100)	2/2 (100)

^a From the 1st TIGC diagnosis. ^b From previous TIGC finding.

Discussion

This single-center prospective study shows that endoscopic follow-up with lesion resection is a safe and effective management for TIGCs: 100% survival, no metastases, no procedure-related complications and early detection of malignant recurring carcinoids developed during follow-up.

A further response provided by this study is that TIGC is a highly recurring disease, as 63.6% of patients enrolled had a subsequent recurrence and 66.6% of them had more than one recurrence; recurrence rate has been poorly described and no prospective study evaluating it has been carried out so far.

Data from this paper also show that TIGCs are frequently represented by small multiple lesions of gastric body/fundus and that during follow-up they can change behavior, becoming less-differentiated and with high proliferation rate. These observations correspond with a few other malignant cases described in previous papers, and have been debated as mostly derived from retrospective, multicenter studies, in small series [9, 11, 13–15].

The evaluation of TIGC biological behavior and the possibility to standardize their management have been difficult up to now, as most of the previous studies were based on small case series, retrospective, multicenter or including all GC types, analyzing tumors with different prognosis all together [2, 5, 9, 11, 13–15].

Some authors recommend surgery as the only treatment capable of avoiding neoplastic progression and definitively solving hypergastrinemia [20, 22]. Proposals of TIGC management also include programs with different treatments according to TIGC number and size, performing surgery in cases of large polyps or frequently recurring multiple lesions, thus limiting a conservative ap-

proach to non-recurring cases of few small TIGCs [20, 39]. On the other hand, promising results have been reported by SAs in selected patients having small multiple TIGCs without any sign of invasion [9, 23–27].

A further option is a conservative approach by endoscopic monitoring and TIGC resection, but data supporting its efficacy and resulting from prospective large series and long follow-up are lacking [18, 28–29]. According to TIGC's generally indolent behavior, other studies have proposed to manage them just by observation, limiting resection to larger polyps with signs of spread [19, 40]. However, ABG patients are at risk also to develop adenocarcinoma, thus endoscopic resection of 'any' gastric polyp found is justified; annual incidence of adenocarcinoma for these patients is of 0.25% in the case of intestinal metaplasia, 0.6% when mild or moderate dysplasia are present, 6% in the case of severe dysplasia [41–42].

The first endpoint of this study was the clinical outcome of TIGC patients managed by endoscopic approach, showing a 100% survival rate in a median 4 year-follow-up and no evidence of local spread or lymph node/distant metastases. These findings suggest that the conservative approach is effective, and as no patient had any postendoscopic complication or need for hospitalization, it is also safe. Conversely, surgery-related morbidity and negative influence on patients' long-term quality of life should be considered.

Surgery must be limited to the few cases of malignant lesions (gastric adenocarcinoma or poorly differentiated NET) detected during follow-up. One recurring patient of our case series showed a highly proliferating NET, and was treated after histological and EUS evaluation by total gastrectomy with lymphadenectomy. This is a possible risk for recurring patients, but a strict follow-up also has the advantage of not missing these cases, of detecting and treating them early by surgery, thus avoiding the need of any adjuvant treatment.

TIGCs can also be represented by intramucosal carcinoids. As they are not macroscopically visible, we cannot exclude that they are not real recurrences, but that they were already present at the previous endoscopy. In these patients, therefore, a complete bioptic gastric map should be performed during every EGD to increase the probability of detecting intramucosal carcinoids [4, 43].

It has been reported that TIGCs are usually associated with moderate/severe corpus predominant atrophic gastritis, but they may also occur in mild atrophy [11, 24]. Even though the majority of our patients were affected by severe atrophy, TIGC development was also associated with mild atrophy (18.2% of cases). The same observation

can be applied to ECL cells pattern, as the sole presence of simple or linear hyperplasia was associated to TIGC. This figure is consistent with previous observations performed in smaller series, reporting the possibility of TIGC also with simple/linear hyperplasia [14].

Our secondary endpoint was the evaluation of TIGC recurrence rate. Of this case series, 67.6% showed subsequent carcinoid findings after initial tumor resection. Interestingly, recurrence was mostly observed during early follow-up, median RFS being 24 months. This result may suggest that these tumors have a high recurrence rate; however, as TIGCs are often multiple and small, or even intramucosal carcinoids, we cannot exclude that these early recurring lesions were already present at diagnosis, missed at previous endoscopy and not resected. By planning the first endoscopic control after 6 months, TIGC eradication can, however, be completed. Moreover, 66.6% of these patients had at least another TIGC finding during follow-up, thus being certainly considered as recurrences. Endoscopic approach with 6- to 12-month controls is safe and effective also for them, and shows a good compliance. For non-recurring patients, endoscopic controls might be planned yearly in the early follow-up, but can probably become less intensive with EGD every 2–4 years according to ABG screening for adenocarcinoma [36].

In these highly recurring patients, it would be useful to identify risk factors for recurrence at the first diagnosis, reserving a strict endoscopic follow-up program for them. Even though anemia and severe atrophy were more present in patients with recurrence than in patients with no recurrences (85.7 vs. 58.3%; 71.4 vs. 50%, respectively), no statistically significant risk factor was found, probably due to the relatively small series.

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This study has some limits, the most important being the low number of patients, the long enrollment period and the relatively short follow-up time for 20-year-old patients. However, due to TIGC rarity, it is difficult to solve these problems unless a prospective multi-center trial is designed. Another limit is linked to the word ‘recurrence’ itself. In fact some patients had intramucosal carcinoids, and as mentioned above their presence since previous EGD cannot be excluded; moreover, removal by forceps used for some small polyps might offer a less complete endoscopic resection, leaving part of the lesion in situ. However, 6-month-interval EGDs seem to be effective to control ECL growth and, if needed, complete eradication, and the different resection techniques showed no influence on recurrence risk analysis.

Conclusions

This study shows that TIGCs have a high recurrence rate and a low but not negligible risk of malignant behavior, that endoscopic management is a safe and effective method in these patients, with a 100% survival rate and early detection of aggressive carcinoids developed during follow-up. However, more studies based on larger series are needed to identify recurrence risk factors for TIGCs.

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