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Intravenous sedation during esophagogastroduodenoscopy is associated with a reduced risk of missed gastric cancer

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Abstract

Purpose Esophagogastroduodenoscopy (EGD) is an effective technique for diagnosing gastric cancer (GC). However, it is estimated that 10% of GCs are unnoticed, constituting missed gastric cancer (MGC). To analyse the incidence of MGC in our area, the characteristics of GC and factors related to MGC were evaluated.

Materials and methods This was a retrospective study of patients diagnosed with GC at a single centre between October 2003 and December 2018. MGC was defined as GC undetected in a EGD performed 3 to 36 months before diagnosis.

Results A total of 333 patients with GC were identified, 6% of whom had MGC. MGC was more frequently located at anastomotic site of a previous surgery ($p=0.001$), and fewer patients with MGC experienced alarm symptoms ($p=0.001$). Using fewer biopsies ($p=0.001$) and performing the procedure without sedation were associated to MGC. According to multivariate analysis, the factors associated with MGC were the absence of sedation [OR 3.2 (95% CI 1-10.4)] and localization in the anastomosis of previous surgery [OR 11.5 (95% CI 1.8–72.8)]. Moreover, there were no differences in 5-year survival between patients with MGC and patients without MGC.

Conclusions The MGC percentage was 6%. When an EGD is indicated, regardless of the symptoms, IV sedation is recommended to reduce the risk of MGC. In addition, biopsies of the anastomosis from previous surgery should be considered even in the absence of clear suspicious lesions.

Keywords Missed gastric cancer, Esophagogastroduodenoscopy, Sedation, Anastomosis

Fernando Fernández-Bañares passed away on Tuesday June 13, 2023.

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Introduction

Gastric cancer (GC) is the fifth most common malignant neoplasm worldwide. According to GLOBOCAN estimates from 2020, gastric cancer accounted for 5.6% of all newly diagnosed cancer cases worldwide, out of a total of 36 new cancer cases across all sites in 185 countries. In the Spanish population, this percentage is lower than 2.5% [1]. Despite this low incidence, GC has a poor prognosis, with a 5-year survival rate that does not exceed 30%, mostly due to an advanced stage at diagnosis [2]. Currently, there is no cost-effective test for the early detection of GC that may be comparable to the faecal occult blood test for the diagnosis of colon cancer. In the absence of a massive and inexpensive non-invasive method, the gold standard technique for the diagnosis of GC is esophagogastroduodenoscopy (EGD), which allows for the possibility of obtaining biopsies of suspicious lesions. To standardize and improve the results of this technique, different scientific societies have established quality criteria for EGD [3–6]. Despite this, a proportion of neoplastic lesions go unnoticed and are known as missed gastric cancer (MGC). According to the known biology of GC, these lesions evolve from early to advanced stages over a period of 3 years [7]. Based on these findings, MGC is generally defined, as GC detected in a patient who had a negative endoscopy performed within the 3 years before the GC diagnosis [8–12]. Studies of MGC in the Asian population have shown percentages of 25%, probably due to the large number of screening procedures performed in this region of the world, which has the highest incidence of GC [13]. In Western countries, MGC is less common, with a prevalence ranging from 1.2 to 20% [9]. In Spain, relevant information is scarce, with two previously published articles reporting a prevalence ranging from 4.7 to 9.1% [11, 12].

Several factors have been associated with MGC. Variously, patients underwent an insufficient number of biopsies (< 6); or had food residue scraps mucus on the gastric surface; or had previous treatment with proton pump inhibitors (PPIs); or had an specific gastric location of the malignant lesions; or lacked warning symptoms; or were affected by some other identifiable factor [9, 11, 14]. In contrast, other factors, such as the use of sedation during the procedure, did not demonstrate a clear effect [15].

Despite the potential delay in diagnosis and its deleterious consequences, no study has demonstrated a worse prognosis in terms of survival in patients with MGC [9–12, 16–18]. This is likely because GC is often diagnosed in advanced stages.

It is important to know the prevalence of MGC and the factors related to it, especially those associated with the endoscopic procedure. This allows us to increase the rate of early recognition and establish better quality indicators for EGD based on these factors.

Thus, we decided to conduct this study to determine the prevalence and survival of patients with MGC in the catch area of a community hospital and to evaluate the factors associated with the unrecognition of a GC.

Materials and methods

Design, study population and data collection

We performed a retrospective observational study to evaluate the prevalence and characteristics of MGC compared to non-MGC patients diagnosed at the Hospital Universitari Mútua Terrassa (Catalonia, northeastern Spain). The population represented in the hospital is of a mixed rural–urban type (250,000 inhabitants, according to the data provided by the health department of the Autonomous Government of Catalonia "CatSalut"). In the catchment area, there is only one hospital for both public and private practice, and the relevant services are only performed in the endoscopy unit and the pathology department. The hospital offers universal coverage for primary and specialist services, with an established system for referral from primary care. There are some private practitioners in the area, but private EGD and biopsies are performed at the same hospital.

The study population included all patients diagnosed with GC identified through the pathology database from October 2003 to December 2018. The clinical and demographic data as well as factors related to the endoscopic procedure were obtained from the patients' electronic clinical records. A total of 351 patients with biopsies positive for GC were identified (adenocarcinoma, lymphoma, and gastrointestinal stromal tumours [GISTs]). Eighteen patients were excluded due to incomplete information or loss to follow-up (Fig. 1). All reports of EGDs performed on patients with GC were reviewed. The study was conducted in accordance with the principles of the Declaration of Helsinki. Data collection and participant involvement were approved by the Ethics Committee of Hospital Universitari Mútua Terrassa (P/22–074, 22 September 2022). The waiver of informed consent was granted in accordance with Article 58 of the Biomedical Research Law 14/2007, due to the impossibility of obtaining consent from the subjects without disproportionate effort and the use of data in terms that do not allow the direct or indirect identification of participants. This waiver was evaluated and favourably approved by the relevant ethics committee.

MGC definition

MGC was considered in any patient with GC who had a prior negative EGD for malignancy performed 3 to 36 months before diagnosis. The following situations were not included in this definition: (1) tumour recurrence in

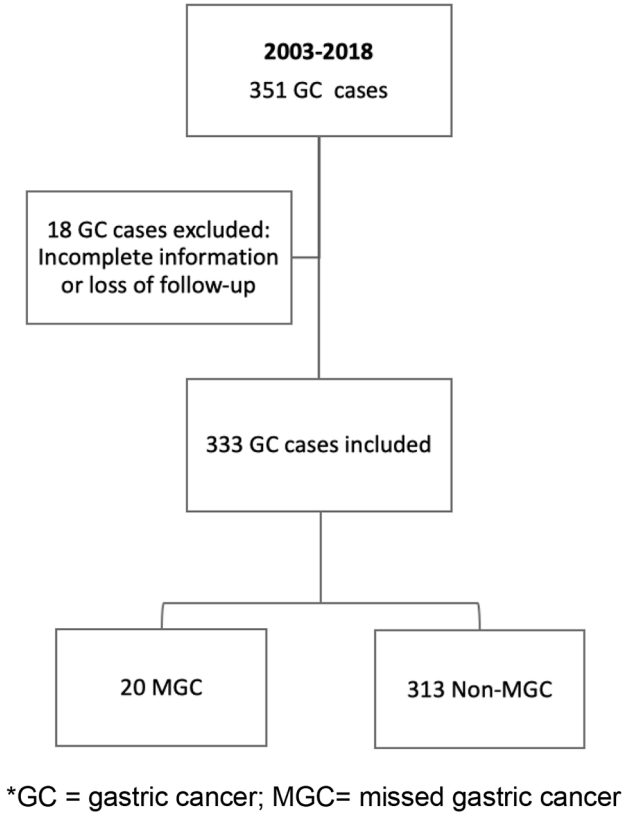


Fig. 1 Study flowchart

endoscopies scheduled for follow-up after GC surgery; (2) GC detected in endoscopic control of a previously detected gastric ulcer within the scheduled time according to guidelines; (3) GC detected in a second endoscopy performed due to a previously improper examination (presence of clots in urgent endoscopy, food residues, etc.); (4) endoscopies with high suspicion of malignant lesions and negative biopsies; and (5) neuroendocrine tumours.

Study variables

Two main cohorts of patients were established: MGC and non-MGC patients. The following clinical and demographic variables were compared between the two groups at the time of EGD: sex, age, smoking habit and clinical symptoms (weight loss, bleeding, anaemia, dysphagia). The tumour-related variables recorded were histologic type, presence of intestinal metaplasia in case of adenocarcinomas, location of the lesion, stage and treatment. A comparison of survival time after surgery between the two cohorts was performed only for adenocarcinoma patients due to the limited number of remaining cancers and different survival times. The therapeutic regimens were classified into the following categories: 1—endoscopic or surgical group; 2—chemical and surgical group; and 3—chemical and/or palliative treatment group. Tumour stage was defined according to the American Joint Committee on Cancer (cTNM) system [19] and was classified into three main groups based on the latest European Guidelines [20]: early (stage IA), potentially resectable (stages IIB-III) and advanced (stage IV). Concerning survival, the medical records of each patient with adenocarcinoma were reviewed, with a minimum of 5 years of follow-up.

The following variables were recorded at the time of diagnostic EGD in both groups and at the first negative EGD in the MGC group: date of the procedure, symptoms, number of biopsies performed, type of endoscope used (high definition, Olympus-GIF-HQ190; or standard definition, Olympus-GIF-Q145/165), presence of residual food, endoscopic findings and use of sedation (local pharyngeal anaesthesia/nothing vs. intravenous sedation—mainly propofol). Sedation was controlled in most cases by endoscopists except for patients with a high anaesthetic risk (ASA III, frailty, etc.), who were managed by anaesthesiologists. The drug used for sedation was propofol, except for patients with contraindications due to comorbidities that were controlled by anaesthesiologists, in which case other drugs were used at the anaesthesiologist's discretion.

Statistical analysis

The results are expressed as the mean (standard deviation (SD)), median (interquartile range (IQR)), percentage (percentages) and 95% confidence interval (CI) when appropriate. For comparing categorical data between the two groups (MGC and non-MGC), the χ^2 test or Fisher exact test was used. Student's t test or its nonparametric counterparts, when necessary, were used to compare quantitative variables. Exploratory analyses to evaluate factors associated with MGC were performed by means of bivariate and multivariate logistic regression analysis. Clinical, demographic and EGD-related factors that were statistically significant in the univariate analyses were included in the multivariate analysis. The odds ratio (OR) and 95% CI were calculated to assess the strength of each association. The overall survival of the two groups (MGC and non-MGC) was calculated using the Kaplan–Meier test and compared by means of the log rank test. The significance level for statistical decisions was set to 5%. SPSS 25.0 software (SPSS Software, SPSS, Inc., Chicago, IL) was used.

Results

MGC prevalence and general characteristics

A total of 333 patients with GC were analysed during the 15-year study period. Twenty patients met the criteria for MGC, representing an MGC rate of 6%. Thus, the MGC and non-MGC cohorts included 20 and 313 patients, respectively. No differences in clinical or demographic

characteristics were detected between the two groups, except for the absence of alarm symptoms at the time of negative endoscopy in the MGC group compared with the diagnostic endoscopy in the non-MGC group (Table 1). The mean age of the patients with GC was 70 years (SD, 13.8); most patients were male (66.3%), while 40% were smokers. The most frequent histological type in both groups was adenocarcinoma. In the MGC cohort, 2 patients (10%) had GISTs, and in the non-MGC cohort, lymphoma was the second most common type of tumour (8.3%). A detailed description of clinical and pathological characteristic of patients with MGC is provided in Table 2.

Regarding location, lesions in the MGC patients were less frequently detected in the body-antrum (50% vs. 75.1%; $p = 0.014$) than in the non-MGC group, and lesions were more common at the anastomotic site of previous gastric surgeries (15% vs. 1%; $p = 0.001$) (Fig. 2) Surgeries were performed due to peptic ulcers in all except one case (Case 17; Table 2) with gastrointestinal jejunostomy of Billroth type I and II being the most common surgeries. Case 17 had undergone a partial gastrectomy with Roux-en-Y reconstruction due to gastric adenocarcinoma and one year later a recurrence was missed at EGD, being diagnosed 8 months later because of constitutional symptoms. No case of metachronous CG was detected.

Regarding the presence of intestinal metaplasia, that is a local predisposing factor for adenocarcinoma, no differences were found between the two groups (72.7% vs. 74.7%, $p = 0.841$).

Table 1 Clinical and demographic characteristics of all GCs ($n = 333$)

	Non-MGC ($n = 313$)	MGC ($N = 20$)	*p*
Sex; Male; n (%)	207 (66.1)	14 (70)	0.723
Age; mean (SD)	70 (14.1)	71.7 (10.5)	0.598
Alarm symptoms; n (%)	231 (73.8)	6 (30)*	0.001
	231 (73.8)	14(70)**	0.708
Histology; n (%)			0.130
Adenocarcinoma♦	277 (88.4)	18 (90)	
Lymphoma	26 (8.3)	0 (0)	
GIST	10 (3.3)	2 (10)	
Location; n (%)			0.001
Body-antrum	235 (75.1)	10 (50)	0.014
Cardia-fundus	66 (21)	5 (25)	0.348
Anastomosis	3 (1)	3 (15)	0.001
Diffuse	9 (2.9)	2 (10)	0.084
Smokers[Δ]; n	269	18	0.375
Yes, n (%)	106 (39.4)	9 (50)	
No, n (%)	163 (60.6)	9 (50)	
Intestinal metaplasia[Δ▽]; n	277	11	0.841
Yes, n (%)	207 (74.7)	8 (72.7)	
No, n (%)	70 (25.3)	3 (27.3)	

GC = gastric cancer; MGC = missed gastric cancer; SD = standard deviation; GIST = gastrointestinal stromal tumour

*Alarm symptoms at the time of *negative* endoscopy

**Alarm symptoms at the time of *diagnostic* endoscopy

♦Diffuse and intestinal adenocarcinomas (Lauren classification)

[Δ]*Information on all patients was not available*

[▽]Only for adenocarcinomas

Factors depending on the endoscopic procedure

To identify what could impact the ability to overlook a GC during an endoscopic procedure, we compared factors related to a successful diagnosis in the non-MGC group with those related to the first negative EGD in the MGC group (Table 3). According to univariate analysis, in the MGC group a significantly fewer number of biopsies were taken (1.95 ± 2.3 vs. 4.98 ± 2.2, $p = 0.001$) and a lower rate of intravenous sedation (20% vs. 46.3%, $p = 0.022$) was used at EGD compared to the non-MGC group. In fact, a greater but nonsignificant trend of MGC was also observed during the 2003–2013 period, in which endoscopies were performed mostly without sedation, than during the 2014–2018 period when endoscopies were performed mainly with sedation (6.8% vs. 4.3%). Table 2 shows the characteristics of both the negative and diagnostic EGD in the MGC group. The median delay from previous negative endoscopy to GC diagnosis was 14 months (IQR 3–36).

Predictor factors for MGC

The following factors showing statistically significant relationship with MGC in the univariate analysis were introduced in the logistic model: the presence of alarm symptoms, the location in anastomotic site and the use of sedation. An endoscopic procedure without IV sedation (OR 3.2, 95% CI 1-10.4; $p = 0.044$) and location of the lesions at the site of previous gastric surgery (OR 11.5, 95% CI 1.8–72.8; $p = 0.009$) were the only factors independently associated with MGC.

Treatment and prognosis of adenocarcinomas

Data regarding staging and treatment administered were available for 89% and 96%, respectively, of the adenocarcinoma patients ($n = 295$). The most common tumour stage in both groups was potentially resectable (IB-III), but the most common treatment was chemotherapy and/or supportive treatment with palliative intention (Table 4). Moreover, there were no differences in the one-, three- or five-year survival rates between the MGC and non-MGC patients (Fig. 3). No difference was found in survival rates at the end of the follow-up. The mean survival time at the end of the follow-up was 78.6 months (SD, 27.3) in patients with MGC and 95.5 months (SD, 7.3) in patients without MGC ($p = 0.507$). The survival analysis results are summarized in Fig. 3.

Table 2 Characteristics of patients in the MGC group with previous negative results and diagnostic endoscopy results

N°	Previous gastric surgery	Previous negative EGD			Time until diagnosis (months)	Diagnostic EGD		
		Findings	Biopsies: No/Yes (*N°*)	Pathology results		Tumor histopathology	Tumour localization	Indication
1	No	Hyperplastic polyp in fundus	Yes	Hyperplastic polyp	23	Adenocarcinoma	Antrum	Epigastralgia
2	No	Pangastritis	Yes	Chronic atrophic gastritis	24	Adenocarcinoma	Antrum	Control
3	Billroth I	Multiple irregular ulcers in antrum and duodenum	Yes (4)	Acute inflammation and granulation tissue	6	GIST	Body	Control
4	No	Slightly enlarged gastric folds	Yes (2)	Chronic gastritis, *H pylori* positive	7	Adenocarcinoma	Diffuse	Weight loss epigastralgia
5	No	Slightly granular gastric mucosa and bile reflux	Yes (3)	Reactive gastropathy	5	Adenocarcinoma	Fundus	Enlarged gastric folds in TC
6	No	Erosive anthritis	Yes (2)	Chronic gastritis, *H pylori* positive	16	Adenocarcinoma	Fundus	Epigastralgia
7	Billroth II	Erythaematous mucosa in anastomosis and bile reflux	Yes (2)	Chronic inflammation	3	Adenocarcinoma	Anastomosis	Abdominal mass
8	Billroth II	Erythaematous mucosa in anastomosis	No	-	23	Adenocarcinoma	Anastomosis	Bleeding
9	No	Benign-looking ulcer in gastric body	Yes (10)	Chronic atrophic gastritis	7	Adenocarcinoma	Body	Bleeding
10	No	Pseudopediculated polyp in antrum	No	-	28	Adenocarcinoma	Antrum	Anaemia
11	No	Atrophic gastritis in antrum	Yes (4)	Chronic atrophic gastritis and intestinal metaplasia	26	Adenocarcinoma	Antrum	Epigastralgia
12	No	Ulcer in hernial buckle (3 mm)	Yes (2)	Chronic gastritis	31	Adenocarcinoma	Body	Bleeding
13	No	Atrophic gastritis and erythematous antral mucosa	Yes (1)	Chronic gastritis, H *pylori* positive	36	Adenocarcinoma	Cardias	Weight loss Epigastralgia
14	Billroth I	Erythematous mucosa in anastomosis and bile reflux	No	-	10	Adenocarcinoma	Fundus	Weight loss Epigastralgia
15	No	Normal	No	-	36	Adenocarcinoma	Antrum	Bleeding
16	Distal oesophagectomy	Normal (no stomach lesions)	No	-	11	Adenocarcinoma	Diffuse	Dysphagia
17	Partial gastrectomy with Y Roux reconstruction	Anastomosis without lesions	Yes (2)	Atrophic gastritis	8	Adenocarcinoma	Anastomosis	Weight loss
18	No	Erythematous antritis	Yes (3)	Chronic atrophic gastritis and intestinal metaplasia	12	Adenocarcinoma	Body	Bleeding
19	Billroth I	Erythematous mucosa in anastomosis and bile reflux	Yes (2)	Chronic gastritis	3	GIST	Fundus	Abdominal mass
20	No	Benign-looking antral ulcer	Yes (2)	Chronic atrophic gastritis and intestinal metaplasia	34	Adenocarcinoma	Body	Anaemia

MGC = missed gastric cancer; EGD = Esophagogastroduodenoscopy; GIST = gastrointestinal stromal tumour

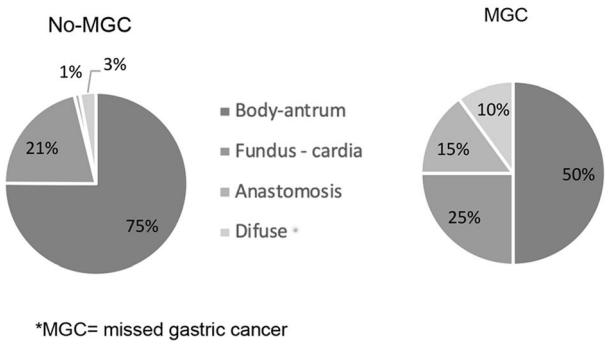


Fig. 2 Tumour location in the two groups (non-MGC and MGC) ($p < 0.001$)

Table 3 Characteristics of first negative EGD procedure in MGC patients compared to non-MGC

	Non-MGC (*n* = 313)	MGC (*n* = 20)	*p*
Presence of residual food; n (%)	13 (4.2)	2 (10)	0.222
Endoscopes; n (%)			0.235
Olympus-GIF-Q145/165	198 (63.3)	10 (50)	
Olympus-GIF-HQ190	115 (36.7)	10 (50)	
Number of biopsies; mean (SD)	4.98 (2.2)	1.95 (2.3)	0.001
IV Sedation; n (%)	145 (46.3)	4 (20)	0.022

EGD = Esophagogastroduodenoscopy; MGC = missed gastric cancer; SD = standard deviation; IV = intravenous

Table 4 Stage and treatment of patients with adenocarcinoma (*n* = 295)

	Non-MGC	MGC	*p*
Stage (*n* = 263*), n (%)			0.684
IA (early)	33 (13.3)	3 (21.4)	
IB-III (potentially resectable)	121 (48.6)	6 (42.9)	
IV (advanced)	95 (38.1)	5 (35.7)	
Treatment (*n* = 283), n (%)**			0.225
Endoscopic resection/Surgery	70 (26.3)	6 (35.3)	
Surgery + chemotherapy	84 (31.6)	2 (11.8)	
Chemotherapy/palliative	112 (42.1)	9 (52.9)	

MGC = *missed Gastric Cancer;* SD = standard deviation

*32 patients with unavailable information

**12 patients with unavailable information

Discussion

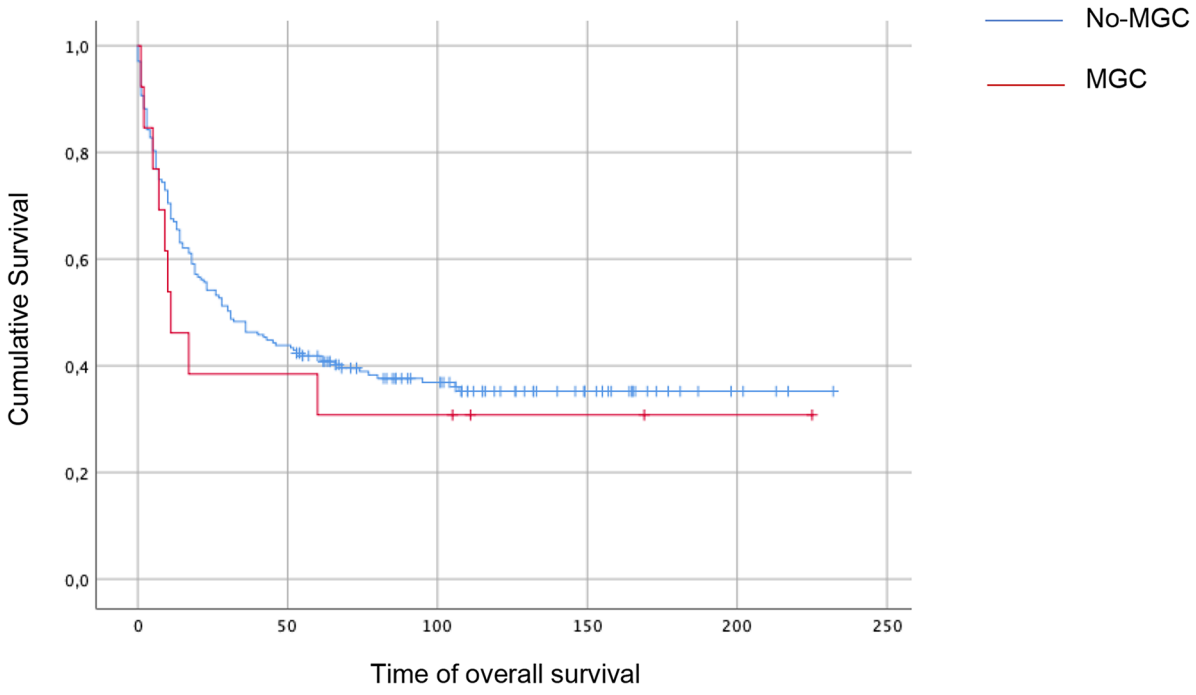
The MGC prevalence in our study was 6%, which is in the lower range of prevalence reported in Spain and other Western countries [9, 11, 12, 14]. Although the definitions of MGC are not consistent across published studies, we considered and applied the most common one, i.e., patients with a previous negative endoscopy performed within the 3 years before the diagnosis of GC [14]. Given that EGD is the gold standard technique for the diagnosis of GC, it is important to know the prevalence of MGC and identify the potentially amendable factors to improve the sensitivity of this diagnostic tool.

In our study, as in others, no differences in the demographic characteristics of the groups were detected. However, in some previous studies, controversial results regarding sex and age were reported to be related to MGC [10, 14, 21].

An important aspect of helping to improve the detection of GC is being aware of the most frequent location of MGC and focusing the inspection on the places where GC goes most unnoticed. Although in our study the body and antrum were the most common tumour locations in both groups, as described in previous studies [9, 11, 12, 14], in the MGC group, a lower percentage of tumours were located in the area where they were more frequently found in the GC group. The anastomotic site at which a previous gastric surgery was performed was independently associated with up to an 11 times higher risk of MGC. Similar results were previously reported in two studies [11, 18]. It is known that the risk of GC increases 6 to 8 times in patients undergoing surgery, particularly in patients with the Billroth II type, and mainly from 15 to 20 years after the procedure [22, 23]. Probably, the hypochlorhydria and biliary reflux, which induce chronic inflammation and decrease in the barrier function of the gastric mucosa, may have a pathogenic role. Some authors have recommended annual endoscopy with random biopsies starting 20 years after surgery but with a low level of scientific evidence [24]. On the other hand, tumours arising at the anastomotic site have a poor prognosis [25]. Therefore, it is essential in these patients to perform an accurate examination of the anastomosis of previous surgery and it is recommended to obtain multiple biopsy samples, even if there are no macroscopic lesions suspicious for malignancy.

Regarding the clinical factors, it is important to highlight that MGC patients had significantly fewer symptoms at the time of the first EGD (30 vs. 73.8%), as previously reported [11, 16, 17]. However, the proportion of patients with alarm symptoms increased to 70% at the time of diagnostic EGD in the MGC group, a proportion similar to that observed in the non-MGC group. This could be explained by the fact that more locally advanced lesions are likely more symptomatic. In addition, endoscopists are likely more aware of malignant lesions in patients with warning symptoms because they are expecting to find them. Therefore, it is essential to perform a careful endoscopy even in patients without classic "alarm" features.

Therefore, both the location and clinical presentation are factors that facilitate GC diagnosis via endoscopic examination. However, accurate examination and systematization of EGD must be mandatory in all endoscopy units, regardless of their indications, to improve the detection of malignant lesions and avoid MGC.



MGC=missed gastric cancer
**79 patients for whom information was unavailable were excluded (75 from the non-MGC group and 4 from the MGC group)*

	1-YEAR	3-YEARS	5-YEARS	END FOLLOW-UP
MGC %(CI)	46% (15-78)	38% (8-69)	38.46% (7.86-69,06)	31% (2-60)
NON-MGC %(CI)	67% (60-74)	46% (39-53)	38.42% (31.68-45.17)	37% (30-44)
p	0.125	0.58	1	0.887

Fig. 3 Survival analysis of patients with adenocarcinoma: comparison between non-MGC and MGC patients ($n=216$*)

The absence of food debris is one of the multiple quality indicators established in the different guidelines [3, 5, 26], and it is a factor that may obviously impact GC detection. We did not find differences because the percentage of patients with food debris was low in both groups owing to the endoscopy generally being rescheduled in cases of improper preparation.

Regarding the factors associated with the endoscopic procedure, it is known that IV sedation is considered an important quality indicator of EGD and is recommended by all guidelines despite the lack of evidence supporting this assertion [3–6, 26]. To our knowledge, this is the first study to demonstrate that performing endoscopy without sedation is an independent factor associated to the presence of MGC, with an OR of 3.2. This could be explained by the fact that the use of sedation, which has been demonstrated to be safe in endoscopic units [27], undoubtedly improves patient tolerance of the procedure and the comfort of endoscopists, allowing a more accurate examination of the entire gastric cavity. However, we emphasize that this relationship is based on an association observed in our study and does not imply a direct causality, given the observational design of the study. In only one study performed in a single centre in the United Kingdom there was no relationship between sedation and MGC [15]. In addition, in another study, MGC was related to endoscopies performed in primary care without sedation [28]. Although performing EGD without sedation likely has a negative impact, it should be considered that other factors could be linked to both sedation

usage and diagnostic accuracy. For example, more experienced endoscopists, more meticulous exams might coincidentally be more likely when sedation is used, rather than sedation alone being the protective factor. We also detected a decrease of more than 2% in the incidence of MGC in the period 2014–2018, during which sedation was routinely established for all digestive endoscopies. Although this difference did not reach significance, this suggests a time trend that aligns with multiple factors that improved endoscopic technique including sedation and perhaps better training or equipment.

Although we did not find that performing endoscopies with high-definition endoscopes contributed to a decrease in MGC incidence, the use of high-definition endoscopies with magnification techniques and chromoendoscopy helps to detect premalignant lesions such as metaplasia and dysplasia [29]. However, this has not yet been reflected in a higher rate of detection of early gastric adenocarcinoma [30]. These lesions are still uncommon in our geographical area, most likely due to their low incidence and therefore due to the steep learning curve for their detection [31].

Finally, in those patients with adenocarcinoma, we did not find any differences regarding the stage, therapeutic schedule, or survival between the two groups as has been reported in all previous studies [9, 11, 12]. This is likely because, as mentioned before, GC is still diagnosed in advanced stages, and a delay in early diagnosis does not imply any difference. However, this approach is expected to change with the use of new mucosal assessment techniques, such as magnification or vital or virtual chromoendoscopy, which could help us diagnose lesions in earlier stages [29]. Although most of the patients in our study had potentially resectable GC, the most common treatment was chemotherapy or palliative care. This can be explained by the existence of comorbidities, including advanced age. Therefore, aggressive curative approaches, such as surgery, were not performed, and complete staging was considered unnecessary.

The most important limitation of this study is its retrospective nature, which implies that certain relevant information may have been missing or that some data were incomplete, such as gastric content (no scales were used [32]), the experience of the endoscopist, duration of the procedure, withdrawal time, previous use of PPIs/NSAIDs or the presence of *Helicobacter pylori*. In addition, the sample size of MGC cases is small, which may affect the statistical power of the analysis. Furthermore, the study may be underpowered to detect more modest risk factors, as some variables may have been excluded in the multivariate analysis due to sample size constraints. Therefore, while the identified trends are plausible, they should be interpreted with caution and confirmed in larger prospective studies.

The findings of this study should be interpreted within the context of a region with low incidence of GC and that has been performed in a single-center with universal access to a unified health system where IV sedation, using mainly propofol, is routinely available and safely administered. Therefore, it is important to note that outcomes may differ in other healthcare systems, with other lighter sedation, or in countries with a high incidence of GC.

Another limitation of our study that cannot go unnoticed is the heterogeneity of gastric tumours. We used the definition of MGC for all histological types as reported in the published literature [17, 28]. However, the detectability and miss rates may vary depending on the tumor type, lymphomas or submucosal tumors like GISTs might be more challenging to detect endoscopically. Despite there were no significant differences in the MGC rate between histological types, the majority of MGC cases were adenocarcinomas and our conclusions are primarily applicable to this histological type. Another limitation associated with the definition of MGC is that using the 3-year cutoff implies assuming that the cancer was present but missed on the prior exam, rather than truly absent and newly arisen. While this limitation is inherent to all MGC studies, the three-year cutoff remains a pragmatic choice based on current epidemiological evidence regarding GC progression.

In conclusion, the MGC rate in our study was 6%. Regardless of the symptoms, when an EGD is indicated, we recommend that it be performed under IV sedation with precise visualization of the entire stomach and include multiple biopsies from the anastomotic sites in patients with previous surgery.

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Author contributions
C.L.—design of the study, study coordination, acquisition of data, statistical analysis and interpretation of the data, manuscript writing, critical revision of the manuscript, and approval of the final draft as submitted; I.S., B.A.—study coordination, acquisition of data, statistical analysis and interpretation of the data, manuscript writing, critical revision of the manuscript, and approval of the final draft as submitted; X.A.—acquisition of the data, statistical analysis and interpretation of the data, critical revision of the manuscript, and approval of the final draft as submitted; F.FB., M.E.—statistical analysis and interpretation of the data, critical revision of the manuscript, and approval of the final draft as submitted; C.F., Y.Z., L.R. and M.A.—acquisition of data and approval of the final draft as submittedAll the authors approved the final version of the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author, Carme Loras, upon reasonable request.

Declarations

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee Hospital Universitari Mútua Terrassa (P/22–074) on September 22nd, 2022, with the need for written informed consent waived.

Consent to participate

Informed consent for information published in this article was not obtained due to the impossibility of obtaining consent from the subjects without disproportionate effort and the use of data in terms that do not allow the direct or indirect identification of participants. The waiver of informed consent was granted in accordance with Article 58 of the Biomedical Research Law 14/2007, and was evaluated and favorably approved by the relevant ethics committee.

Consent for publication

Not applicable.

Competing interests

C.L. has served as a speaker for Boston Scientific and consulting fees from Fujifilm. M.E. reports grants and personal fees from AbbVie and Jansen as well as travel grants for educational and scientific meetings from AbbVie, Takeda and Ferring, outside the submitted work. Y.Z. has received support for conference attendance, speaker fees, research support and consulting fees from AbbVie, Adacyte, Dr Falk Pharma, FAES Pharma, Ferring, Janssen, Pfizer, Takeda, Galapagos, Boehringer Ingelheim and Tillots.

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