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Characteristics and consequences of missed gastric cancer: A multicentric cohort study

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ABSTRACT

Background: Missed gastric cancer (MGC) is poorly documented in Mediterranean populations.
Aims: (1) To assess the rate, predictors and survival of MGC. (2) To compare MGC and non-MGC tumors.
Methods: This is a retrospective-cohort study conducted at four centers. MGC was defined as cancer detected within three years after negative esophagogastroduodenoscopy. Gastric adenocarcinomas diagnosed between 2008–2015 were included. Patients with no follow-up were excluded.
Results: During the study period 123,395 esophagogastroduodenoscopies were performed, with 1374 gastric cancers being diagnosed (1.1%). A total of 1289 gastric cancers were finally included. The overall rate of MGC was 4.7% (61/1289, 3.7–6%). A negative esophagogastroduodenoscopy in MGC patients was independently associated with PPI therapy ($p < 0.001$), previous Billroth II anastomosis ($p = 0.002$), and lack of alarm symptoms ($p < 0.001$). The most frequent location for MGC was the gastric body(52.4%). MGCs were smaller than non-MGCs (31 vs 41 mm, $p = 0.047$), more often flat or depressed ($p = 0.003$) and less likely to be encountered as advanced disease. Overall 2-year survival was similar between MGC (34.1%) and Non-MGC (35.3 %) ($p = 0.59$).
Conclusion: MGC accounted for nearly five percent of newly-diagnosed gastric adenocarcinomas. Overall survival was poor and not different between MGC and non-MGC.

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer-specific death worldwide [1]. Despite significant improvements in diagnostic techniques and therapy, the disease is often diagnosed at an advanced stage and only 30% of cases are candidates for curative-intent treatment in recent European cohorts [2]. Conversely, five-year survival rates of above 70% for localized disease have been reported in Eastern countries with screening population programs, underlining the importance of early diagnosis [3].

Esophagogastroduodenoscopy (EGD) with biopsy remains as the gold standard for the diagnosis of gastrointestinal neoplasms. However, several observational studies and meta-analysis addressing colorectal interval cancer have revealed that up to 9% of the tumours were missed in a previous colonoscopy [4]. The information regarding missed upper gastrointestinal tumours is scarce and mostly arising from Eastern countries. Early GC may present

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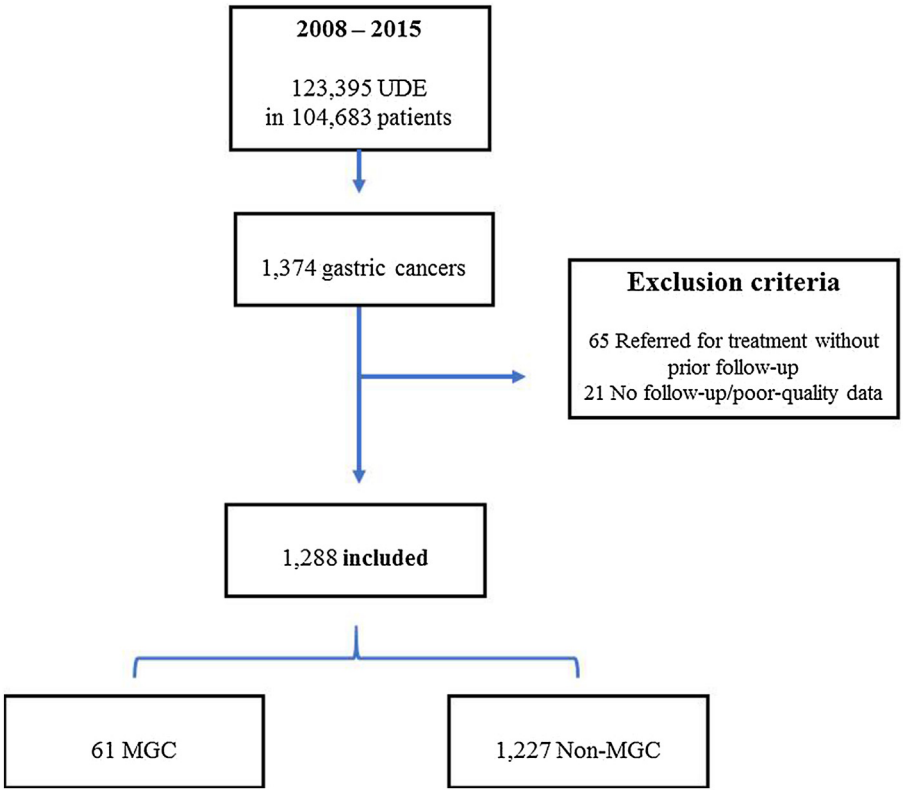


Fig. 1. Study flowchart. EGD = Esophagogastroduodenoscopy. MGC = Missed gastric cancer.

as subtle mucosal abnormalities and can easily go unnoticed during EGD, especially in low-incidence areas where endoscopists are not familiar with this entity. It has been suggested that the rate of missed gastric cancer (MGC) range from 4.6% to 14.3% in Western countries [5–12]. Nevertheless, only few retrospective studies from the UK, Australia, US and Finland have been published in this area [5–12]. It is known that GC epidemiology, treatment modalities and outcomes differ between Northern and Southern Europe [13]. In addition, these studies were limited by being single-centre and frequently with data coming from administrative databases [5–12].

Hence, the aims of this study were: (1) to assess the rate, predictors and survival of MGC; and (2) to compare the characteristics of MGC patients with those of non-MGC.

2. Materials and methods

This was a retrospective cohort, observational, and analytical study conducted at four tertiary academic hospitals in Spain that provide universal public health care assistance to an area with a population of 1.7 million people. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee for clinical research at the four participating centres. Informed consent for EGD was obtained in all cases. Exemption of individual informed consent for the inclusion in the study was accepted by the Ethics Committee due to the retrospective design.

2.1. Study Population and Procedures

All patients who underwent EGD between January 2008 and December 2015 at any of the participating centres were considered for the study. Inclusion criteria for the study were as follows: (1) Patients with histology proven gastric adenocarcinoma diagnosed during the study period in the participating centres. Exclusion criteria were: (a) Patients referred for treatment from other hospitals with no prior follow-up in any of the participating centres; (b) Patients with no available follow-up (Fig. 1).

Two gastroenterologists independently reviewed paper (hospital) and electronic (hospital and primary healthcare) medical records of all GC subjects at each institution. This search included previous negative EGD performed in other public or private hospitals in the same regions. Demographic (age and sex), clinical data (tobacco and alcohol consumption as binary categories, GC family history, history of *H. pylori* infection before GC diagnosis (positive 13C-urea breath test, urease or gastric biopsy), obesity [defined as >30 kg/m2 body mass index], American Society of Anesthesiologists classification); EGD indication (dysphagia, hematemesis, melena, vomiting and constitutional syndrome were considered alarm symptoms), and proton-pump inhibitor (PPI) therapy at both negative and MGC diagnostic endoscopy.

Gastroscopes used for examination were GIF-Q165, GIF-H180, GIF-H190 (Olympus® Optical, Tokyo, Japan), EG-290KP, EG-294 KP, EG-27I10, EG-29I10, EG–1690K, EG–3490K, EG–2790K (Pentax®, Tokyo, Japan) and EG-530FP, EG-250PES (Fujifilm®, Japan). All procedures were performed or directly supervised by a staff gastroenterologist with expertise in EGD using white light.

Date, sedation, urgent or elective setting, use of conventional and digital chromoendoscopy (Narrow-Band Imaging [NBI], i-scan or Fujinon Intelligent Chromo Endoscopy [FICE] as ascertained by written reports, images and videos), number of biopsies, and main diagnosis were collected from both negative and diagnostic endoscopy records. Size of the lesion, as assessed by the endoscopist (millimetres), ulceration, location (gastroesophageal junction, fundus, body, incisura and antrum) and tumour morphology (depressed, flat or sessile-mass) were obtained from the endoscopy report. When more than one negative EGD was available, the most recent one was selected for the analysis. Main operators were classified as highly experienced (>5 years as a staff

gastroenterologist and >1000 EGD) or less experienced endoscopist (<5 years and <1000 EGD).

Histologic subtype (intestinal or diffuse adenocarcinoma) and grade of differentiation (undifferentiated-poorly or moderately-well differentiated) were also retrieved from pathology reports.

Tumour Stage was determined as per the American Joint Committee on Cancer cTNM system 7th edition [14]. Oncologic treatment was recorded as binary outcomes: neoadjuvant therapy, curative-intent surgery, adjuvant therapy and palliative chemotherapy. Survival status was established using the date of GC diagnosis and the date of death. Survivors were right-censored at the date of the last medical visit (in-hospital or primary healthcare).

2.2. Study endpoints

In line with previous studies, MGC was defined as the proportion of patients with GC who had a negative endoscopy within 36 months of diagnosis. The primary endpoint was to assess the proportion and characteristics of MGC. Secondary endpoints were to evaluate the differences between MGC and Non-MGC and between negative EGD and diagnostic EGD in Non-M^{GC}.

2.3. Statistical analysis

Mean, standard deviation, median and range were calculated for continuous variables and frequency counts and percentages for categorical data. Ninety-five percent confidence intervals (CI) for proportions were calculated by the Wilson method. Data were analyzed using parametric methods for normally distributed continuous data (t-test) and nonparametric methods (Mann–Whitney U test) for non-normally distributed continuous distributions. Chi-squared and Fisher's exact tests were used for categorical data. In order to decrease the risk of type I error, only those variables previously reported as risk factors for upper gastrointestinal missed cancer or with plausible physiopathological relation with MGC were included in the univariate analysis. Multivariate analysis was performed by backward stepwise binomial logistic regression analysis in an attempt to: (1) detect predictors associated with negative gastroscopy when compared to diagnostic EGD in Non-MGC; and (2) identify factors associated with MGC at diagnosis.

Variables with p values < 0.2 in univariate analysis were included in logistic regression models. The area under the Receiver Operating Characteristic curve was calculated with non-parametric analysis to evaluate the discriminative ability of the logistic models. Univariate analysis adjusted for multiple comparisons (Holm's method) was performed to compare ulcers at negative and Non-MGC diagnostic EGD. Additionally, we compared missed cancers diagnosed within the first year and 1–3 years before diagnostic EGD.

One-year and two-year survival probabilities were calculated for MGC and Non-MGC by using the Kaplan–Meier method. The log-rank test was used to assess overall survival differences. All analyses were two-tailed, and p values less than 0.05 were considered significant. All statistical calculations were performed at the promoting institution (Hospital Universitario Ramón y Cajal, Madrid, Spain) using STATA software version 14.1 (StataCorp. Texas, USA).

3. Results

During the study period, 123,395 EGDs in 104,683 patients were performed at the four institutions, and 1374 GC were detected (1.11%, 95% CI: 1.06–1.17%). A total number of 1289 patients with GC, meeting criteria for the study, were finally included in the analysis (Fig. 1). The majority of them were males (87%). Mean age was 74.1 years, standard deviation: 11.2. A total number of 61 MGC were identified (0.005%, 61/123,395 EGD). The global rate of MGC was 4.7% (61/1289, 95% CI: 3.7–6%), without significant differences between centers (6.7%, 3.6%, 4.2%, 4.7%; p = 0.23). None of the patients excluded due to no follow-up had a known negative EGD.

Table 1
Comparative analysis of missed gastric cancer according to the interval between negative and diagnostic endoscopy.

	<1 year	1–3 years	Univariate p values
Number of patients	28	33	
Age years, median ± IQR	74.5 ± 21	72.4 ± 12	0.88
Male sex	19 (67.9%)	18 (54.5%)	0.30
PPI therapy	22 (78.6%)	26 (78.8%)	0.98
Family history of GC	1 (3.6%)	2 (6.6%)	1
Obesity (BMI >30)	2 (1.8%)	2 (2.2%)	1
H. pylori infection	22 (78.6%)	23 (69.7)	0.56
Previous gastric surgery	4 (14.3%)	4 (12.1%)	1
Alarm symptoms	20 (67.9%)	14 (42.4%)	0.12
Sedation	10 (35.7%)	6 (18.2%)	0.15
Tumor location			
GEJ	2 (7.1%)	1 (3.3%)	
Fundus	2	5(15.2%)	
Gastric body	17 (60.7%)	15(45.5%)	
Incisura angularis	2	2 (6.1%)	
Antrum	5 (17.9%)	10(30.3%)	0.57
Morphology			
Depressed	8 (28.6%)	5 (15.2%)	
Flat	8	9(27.3%)	
Sessile-Mass	12 (42.8%)	19(57.6%)	0.38
Histology			
Intestinal	16 (57.1%)	18 (42.4%)	
Diffuse	8 (28.6%)	14 (54.6%)	
Mixed/undetermined	4 (14.2%)	1 (3%)	0.24
Presence of ring-cells	8 (28.6%)	16 (48.5%)	0.11
Grade of differentiation			
Undifferentiated-poorly	15 (53.6%)	14 (42.4%)	
Moderately-well	13 (46.4%)	19 (57.7%)	0.38
Cancer stage			
I	7 (25%)	6 (18.2%)	
II	5 (17.8%)	11 (33.3%)	
III	5	6 (18.2%)	
IV	11 (39.3%)	10 (30.3%)	0.55

IQR = Interquartile range.
GC = Gastric cancer.
PPI = Proton-pump inhibitor.
BMI = Body mass index.
GEJ = Gastroesophageal junction.
MGC = Missed gastric cancer.

3.1. Negative esophagogastroduodenoscopy

Median interval time between negative EGD and MGC diagnosis was 13.1 months (range: 3.1–35.2). Among the 61 patients diagnosed with MGC, 45.9% (28/61) had a negative UGE within one year before GC diagnosis, 24.6% (15/61) within 1–2 years and 29.5% (18/61) within 2–3 years. No significant differences were found between GC diagnosed within <1 year and 1–3 years (Table 1). The median number of negative endoscopies in MGC group was 1 (range: 1–3). The most common findings at negative EGD were gastritis (31/61, 51%), intestinal metaplasia (25/61, 41%), gastric atrophy (19/61, 31.1%), and gastric ulcer (18/61, 29.5%). Twenty-one patients (21/61, 34.4%) had a normal negative EGD. Gastric ulcers detected at negative EGD were smaller (median size: 10 mm vs 30 mm, p = 0.02) and a less often biopsied (p < 0.001) than ulcers in Non-MGC (Table 2). Biopsies at negative EGD were negative for malignancy and endoscopic monitoring was inadequate (>6 months) in all cases.

3.2. Predictors of negative esophagogastroduodenoscopy

Univariate analysis and binomial logistic regression intended to detect predictors of negative EGD are outlined in Table 3.

Table 2
Findings at negative endoscopy (n = 61).

	n (%)
Gastritis	31 (51%)
Intestinal metaplasia	25 (41%)
Gastric atrophy	19 (31.1%)
Gastric ulcer	18 (29.5%)
Food residue	5 (8.2%)
Gastric erosion	4 (6.5%)
Polyp	4 (6.5%)
Normal	21/61 (34.4%)

Subanalysis of Gastric ulcers

Variable	Negative EGD (n= 18)	Non-MGC (n = 610)	p Value
Size (mm)[a]	10 (0.3–3)	30 (0.5–7.1)	0.02
Median number of biopsies[a]	1 (0–6)	3.5 (1–13)	<0.001
Location			
GEJ	1 (5.5%)	30 (4.9%)	
Fundus	1 (5.5%)	37 (6.1%)	
Body	9 (50%)	317 (51.9%)	
Incisura	2 (11.1%)	42 (6.9%)	
Antrum	5 (27.7%)	184 (30.1%)	n.s

GEJ = Gastroesophageal junction.
n.s = non significant.
[a] Quantitative values are expressed as median and ranges.

Younger age (OR: 0.96, p = 0.001), PPI therapy (OR: 5.7, p < 0.001) and previous Billroth II anastomosis (OR: 5.2, p = 0.002) were independently associated with a prior negative EGD. Alarm symptoms were present in 47.5% of the patients, but in a lower proportion than at non-MGC diagnosis (OR: 0.21, p < 0.001).

3.3. Factors associated with missed gastric cancer at diagnosis

The second model was estimated to identify factors associated with MGC at diagnosis and it is detailed in Table 4. MGC tumors were smaller than non-MGC (Median size: 31 mm vs 41 mm, OR: 0.98, p = 0.047), more often diagnosed as depressed or flat lesions (OR: 0.3, p = 0.003), and less likely to be encountered as III–IV cTNM stage (52.6% vs 71.7%, OR: 0.44, p = 0.023). The presence of alarm symptoms was less common in MGC patients compared with Non-MGC group (55.7% vs 78.5%, OR: 0.28, p < 0.001).

3.4. Survival analysis

There was no difference in overall survival between the MGC and non-MGC. Survival analysis is summarised in Fig. 2.

4. Discussion

Our study represents the first report from Southern Europe and supports that MGC accounts for a significant proportion of GC (4.7%) at tertiary referral centres. The rate of MGC of our cohort was in line with previous research in this field in Western countries (4.6–14.3%, Supplementary Table) [5–12]. It is important to remark the lack of a formal definition for MGC with substantial heterogeneity across the authors. Based on the landmark study by Fujita [15] suggest-

Table 3
Comparative analysis: initial negative endoscopy in MGC patients vs Diagnostic endoscopy in Non-MGC patients.

	Initial negative endoscopy in MGC patients (n = 61)	Diagnostic endoscopy in Non-MGC patients (n = 1228)	Univariant (p values)	Binomial logistic regression P-Hosmer-Lemeshow = 0.28 AUC = 0.82
Age years, (mean)	69.3	74.3	**0.0007**	**OR = 0.96 (CI 95%: 0.94–0.98), p = 0.001**
Male sex	60.6%	61.6%	0.88	
PPI therapy	78.7%	46.3%	**<0.001**	**OR = 5.72 (CI 95%: 2.9–11.1), p < 0.001**
Smoking habit	48.3%	43.3%	0.443	
Alcohol	20%	21.6%	0.76	
Family history of GC	3.9%	7.6%	0.42	
Obesity (BMI>30)	6.6%	15.6%	0.055	
H. pylori infection	73.7%	62.3%	0.082	
Previous gastric surgery				
No	86.7%	95.3%		
Billroth I	3.3%	1.6%		
Billroth II	10%	2.4%		
Roux-Y-Anastomosis	0%	0.75%	**0.012**	**OR = 5.2 (CI 95%: 1.9–14.6), p = 0.002**
ASA				
I	15%	11.2%		
II	35.2%	33.3%		
III	53.5%	51.7%	0.67	
Elective endoscopy	87.3%	86.6%	1	
Alarm symptoms	47.5%	78.5%	**<0.001**	**OR = 0.21 (CI 95%: 0.12–0.37), p < 0.001**
No	52.5%	21.5%		
Constitutional syndrome	17.4%	29.7%		
Dysphagia	2%	9.3%		
Hematemesis	12%	5.4%		
Melaenas	9.5%	10%		
Other	7.5%	23.7%		
High-definition endoscope	36.1%	40.7%	0.47	
Conventional chromoendoscopy	4.9%	5.1%	1	
Digital chromoendoscopy	3.3%	5.9%	0.57	
Sedation	26.2%	33%	0.27	
No sedation propofol	73.8%	67%		
EndoscopistNon-propofol	13.1%	15.3%		
endoscopist	8.2%	9.7%		
Anaesthesiologist	4.9%	8%		
Endoscopist experience (<5years)	24.6%	21%	0.5	

AUC = Area under the curve.
PPI = Proton-pump inhibitor.
BMI = Body mass index.
ASA = American Society of Anesthesiologists physical status classification.
MGC = Missed gastric cancer.

Table 4
Comparative analysis: MGC vs Non-MGC at diagnosis.

	MGC (n = 61)	Non-MGC (n = 1228)	Univariant	Binomial logistic regression P-Hosmer-Lemeshow = 0.46 AUC = 0.83
Age years, (mean)	70.6	74.3	0.0130	p > 0.05
Alarm symptoms	55.7%	78.5%	< 0.001	**OR = 0.28 (CI 95%: 0.14–0.56), p < 0.001**
No	44.3%	21.6%		
Constitutional syndrome	11.5%	29.7%		
Dysphagia	6.6%	9.3%		
Hematemesis	9.8%	5.5%		
Melaenas	9.8%	10.1%		
Vomiting	13.1%	12.9%		
Other	4.9%	10.9%		
Median tumor size (mm)	31	41	**0.004**	**OR = 0.98 (CI 95%: 0.96–0.99), p = 0.0471**
Conventional chromoendoscopy	6.2%	5.8%	1	
Digital chromoendoscopy	10.7%	11.3%	1	
Tumor location				
GEJ	4.9%	9.1%		
Fundus	11.5%	8.5%		
Gastric body	52.4%	33.7%		
Incisura angularis	6.5%	8.6%		
Antrum	24.6%	37.2%		
Anastomosis	0%	2.7%	**0.046**	p > 0.05
Pylorus involvement	1.7%	7.7%	**0.12**	p > 0.05
Curvature				
Lesser	70.3%	60.7%		
Major	29.6%	39.3%	0.59	
Morphology				
Depressed	21.3%	10.7%		
Flat	27.9%	18.3%		
Sessile-Mass	50.8%	71%	**0.003**	**OR = 0.3 (CI 95%: 0.13–0.66), p = 0.003**
Gastric ulcer	47.5%	49.7%	0.79	
Histology				
Intestinal	55.6%	42.6%		
Diffuse	36.5%	49.2%		
Mixed/undetermined	8.4%	8.1%	**0.04**	p > 0.05
Presence of Ring-Cells	39.3%	28.9%	**0.08**	p > 0.05
Grade of differentiation				
Undifferentiated-poorly	47.2%	42.1%		
Moderately-well	52.8%	57.1%	0.71	
Neoadyuvant therapy	10.2%	8.9%	0.74	
Curative-intent surgery	53.3%	46.7%	0.3	
Adyuvant therapy	19%	18.2%	0.88	
Palliative chemotherapy	20.3%	20.1%	1	
Cancer stage				
I	21.3%	13%		
II	26.2%	15.3%		
III	18.7%	28.5%		
IV	33.9%	43.2%	**0.016**	p> 0.05
(I–II)	47.4%	28.3%		
(II–IV)	52.6%	71.7%	**0.002**	**OR = 0.44 (CI 95%: 0.22–0.89), p = 0.023**

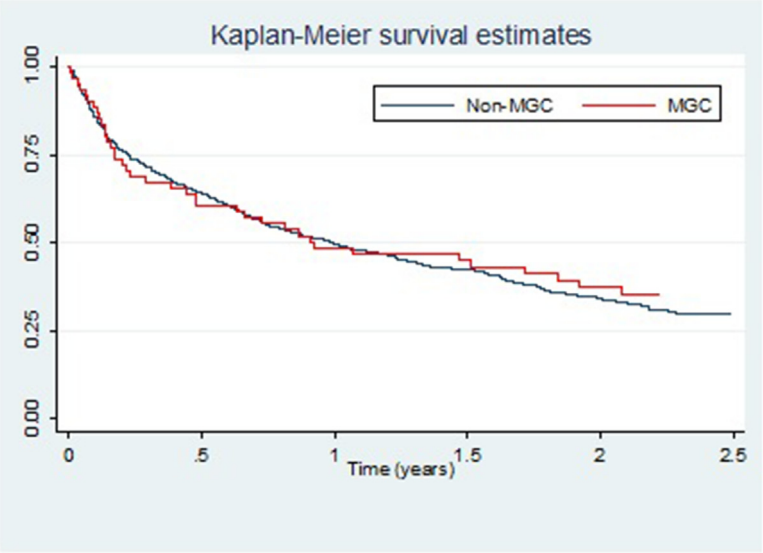
AUC = Area under the curve.
GEJ = gastroesophageal junction.
MGC = Missed gastric cancer.

ing a doubling time of two-three years for GC, the majority of the studies have considered an interval time from six months up to 3.5 years [5–12]. If one assumes that the doubling time for mucosal cancer is two to three years, GC diagnosed within this interval range after a normal endoscopy may well have been missed at the initial EGD. Cancer within the first six months of a negative EGD has been usually excluded since information from administrative databases was not precise enough to determine if these EGDs were part of the work-up [9]. Considering that we had access to detailed medical records, we decided to include all cases with a negative EGD within three years prior to GC diagnosis. Further, we did not detect any significant differences between MGCs diagnosed within the first year and 1–3 years after negative EGD.

We found that PPI treatment was an independent predictor of negative endoscopy ($p < 0.001$). This association may be explained by the partial mucosal healing of small mucosal lesions by PPI therapy and had been described in previous studies [16,17]. Interestingly, this is the first study that has found that previous gastric surgery (Billroth II anastomosis, $p = 0.002$) is independently associated with a prior negative EGD. A possible explanation is that altered anatomy may have contributed to missing a small lesion. Female gender, younger age, non-gastroenterologist endoscopist, and increasing comorbidity have been postulated to increase the probability of missed upper gastrointestinal cancer in previous studies [9–11].

The presence of alarm symptoms was significantly lower at negative EGD. The presence of alarm symptoms was also less common at MGC diagnosis compared with Non-MGC diagnosis (55.7% vs. 78.5%, $p < 0.001$), what is consistent with the fact that MGCs were smaller and diagnosed at a less advanced stage.

It is noteworthy that endoscopy sedation was not associated with MGC. Nonetheless, the low proportion of patients undergoing sedation in our study does not represent the current practice at our institutions where propofol-based sedation has been adopted in the last five years. It has not been proven that sedation decrease MGC rate, but some data indicate that moderate sedation increases EGD examination quality and patient satisfaction [18]. From our perspective, sedation is essential for proper mucosal interrogation, and our negative findings may be related to inadequate statistical power.



Group	1-year survival	2-year survival	Median survival
MGC	46.8% (33.8 – 58.8%)	34.1% (31.4 – 36.9%)	11 (5.9-24) months
Non-MGC	49.6% (46.7 – 52.5%)	35.3% (23.2 – 47.6%)	12 (10.6-14.2) months
Global	49.3% (46.5-52.1%)	34.9% (32.4-37.7%)	11.9 (5.9-14.1) months

Fig. 2. Survival analysis. MGC = Missed gastric cancer.

We found that nearly one out of three patients had a gastric ulcer at negative EGD, some of which could be GCs that were not properly diagnosed. Biopsy policy and endoscopic monitoring did not adhere to clinical guidelines in this subgroup, a fact that has undoubtedly contributed to MGC rate as reported in previous studies [9,12]. Gastric ulcers should be biopsied and re-evaluated after appropriate treatment, including *H. pylori* eradication when indicated, within 6–8 weeks [18]. The sensitivity of cancer diagnosis increases with the number of biopsies, and in the case of a suspected malignancy, at least seven biopsies of the heaped-up edges of the ulcer and base should be performed [19].

In our cohort, MGC were more often encountered as flat or depressed lesions and were smaller than non-MGC, which could have contributed to failure detection at negative endoscopy. Consistent with the available literature, no differences were found in histology subtype or grade of differentiation [5–12]. Stage I was found in only 21.3% of MGC and 70.3% of the patients were diagnosed within <2 years after the negative EGD, what leads us to think that probably most MGC were "true" missed cancer secondary to an unrecognized lesion, although the possibility of new fast-growing lesions remains plausible.

The most frequent location of MGC was the gastric body, but no significant differences with non-MGC were detected. Contrary to colorectal neoplasia where right colon has been consistently proven to be a risk factor for missed cancer [20–23], it does not seem to be a relationship between location and MGC [24].

Another important finding was that despite MGC was more often diagnosed at stage I–II, one-year and two-year survival remained discouraging. This fact emphasises the importance of early diagnosis and the consequences of missing a malignant lesion.

This study has some limitations. First, the observational retrospective design prevented us from gathering some relevant information such as gastric examination time or genetic data. Second, the lack of a nationwide cancer registry database hampered us from ascertaining whether a patient with a negative EGD at our institution have been subsequently diagnosed with GC at other hospitals. We believe that the impact of this bias is expected to be low, since healthcare is public and universal in our country and patients with GC are ordinarily referred to our centres for treatment. Finally, the study may be underpowered for the detection of a small difference in survival due to limited sample size.

Among other strengths of our study are that it identifies new predictors of MGC, provides useful information for clinical practice, and represents a current non administrative-database cohort that may contribute to focus the attention into a relevant but forgotten issue.

In conclusion, MGC represented 4.7% of all GC and probably arose from an undetected early cancer in most cases. PPI therapy and Billroth II anastomosis may contribute to missing malignant lesions. Adequate biopsy sampling, ulcer healing follow-up, and thorough mucosal interrogation are readily available strategies for daily clinical practice that could reduce the rate of MGC and improve GC prognosis in Western countries.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.02.006.

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