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Gastric cancer missed at esophagogastroduodenoscopy in a well-defined Spanish population

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ABSTRACT

Background: Although esophagogastroduodenoscopy (EGD) is the standard procedure for the diagnosis of gastric cancer (GC), some GCs are missed. There are no published data on the missed rate of GC in Spain.
Aims: To determine the frequency and characteristics of missed GCs and assess the quality of the EGD in a specific population with GC.
Methods: Records of all patients diagnosed with gastric adenocarcinoma between 2012 and 2016 in a defined geographic area were reviewed. Missed GC was defined as a case with a prior negative EGD for cancer. Quality indicators from the prior EGDs were measured.
Results: From 212 cases of GC, 25 cases were excluded. Seventeen out of 187 patients had a prior EGD (9.1%). Twelve of those 17 missed GC had a prior EGD with some abnormal findings. In 6 of them, biopsies were taken. Survival was no different between patients with missed and non-missed GC. Quality indicators that failed to meet standards were recording time, image documentation, and a protocol of biopsies.
Conclusions: Missed GC in an EGD in a defined population in Spain is not uncommon (9.1%). The endoscopist is an important factor in missed GC due to lack of adequate detection and sampling error. Compliance with performance of quality indicators could reduce missed GC.

1. Introduction

Gastric cancer (GC) has the sixth highest incident and fatality rates in Spain [1]. The overall 5-year survival is less than 30% because of the advanced stage at diagnosis [2–4].

The most common GCs are adenocarcinomas (>90%), which are the final consequence of premalignant changes such as atrophy, intestinal metaplasia, and dysplasia [5,6]. The evolution from an early to advanced stage may take about 2–3 years [7]. These premalignant changes and the speed of duplication are an opportunity for early detection of GC [8].

Esophagogastroduodenoscopy (EGD) is the standard procedure for detection and diagnosis of GC [9].

Despite efforts to improve GC detection in its early stages, a significant number of cases are not detected in an EGD [10,11]. Previous reports from Western countries indicate that between 4.6% and 14.4% of GCs had a prior negative EGD for GC in the previous 3 years [10–17]. This problem is attributed to several factors, most of them related to technical variables such as rapid exploration, insufficient cleaning of the gastric mucosa, inability to recognize subtle early gastric lesions, or inadequate protocol of biopsies [10–20]. To compensate these limitations, clinical guidelines with quality indicators for the performance of EGD were recently published [21–23].

A number of studies have investigated the GC miss rate, but none has evaluated the quality of the prior negative EGD. In addition, there are no published data from Spain. Therefore, the aim of this study was to study the frequency and characteristics of patients

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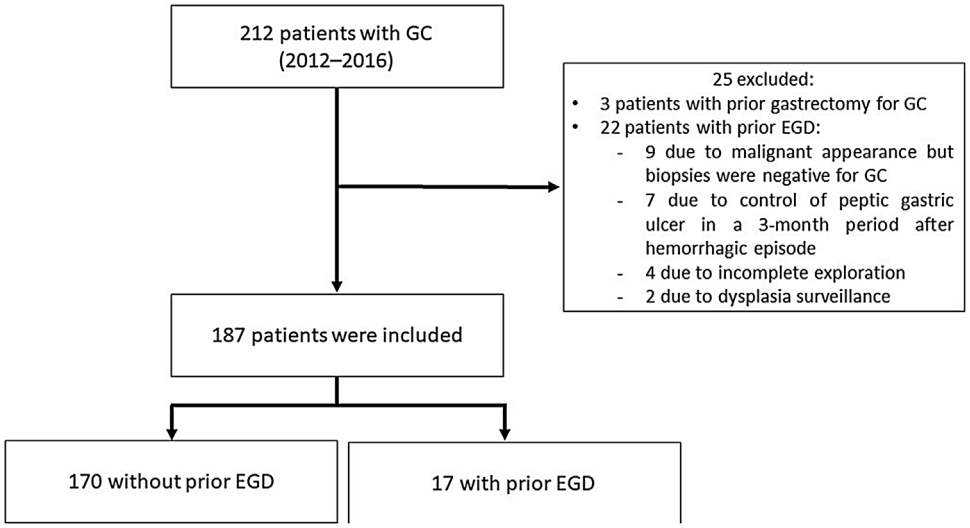

Fig. 1. Patient flowchart. GC: gastric cancer; EGD: esophagogastroduodenoscopy.

with GC in whom the diagnosis was missed in a prior EGD and to assess the quality of the previous EGD based on the indicators proposed by the latest clinical guidelines.

2. Materials and methods

In this retrospective observational study, all patients with proven gastric adenocarcinoma diagnosed with endoscopic biopsies at the Pathology Unit of Hospital General de Granollers between January 2012 and December 2016 were reviewed. We excluded patients in whom the prior EGDs were incomplete, had a suspicion for malignancy that was not confirmed with biopsies, and those enrolled in a cancer surveillance program (dysplasia or peptic gastric ulcer detected 3 months before and patients with a gastrectomy for GC).

Endoscopies were performed by fully trained endoscopists at three community hospitals in a small geographic area (Vallès Oriental, Barcelona) with a mean population of 434,498 inhabitants per year in the period of this study (data provided by Servei Català de la Salud, CatSalut). The study was approved by the Ethics Committee of Hospital General de Granollers.

We defined missed GC as a case in which the prior negative EGD was performed in the previous 3 years before the GC was diagnosed [10].

The following data were collected from the electronic clinical database: demographics, clinical symptoms, *Helicobacter pylori* status, histology, stage and treatment of the GC, endoscopy information, interval between prior negative EGD and diagnosis of cancer, and clinical status at the end of the study (December 31, 2017). Treatment was classified into three categories: (i) curative: endoscopic resection or R0/R1 surgery, (ii) palliative: R2 surgery or chemotherapy/radiotherapy alone, and (iii) comfort: no surgery or chemotherapy/radiotherapy [3,4,24].

2.1. Prior EGD and quality indicators

In patients in whom several EGDs were performed, we considered the most recent negative EGD before the diagnosis of GC. We studied the following indicators: fully trained endoscopist, complete examination, time of exploration, description and location of lesions, biopsies of identified lesions and/or gastric ulcers, biopsies according to the Sydney protocol (when atrophy or intestinal metaplasia was suspected), gastric biopsies (in cases of iron deficiency anemia), and image documentation [21–23]. The frequency of compliance with each of the quality indicator was measured. The reference to assess the quality of the image documentation was the one proposed by Rey and Lambert [25].

2.2. Statistical analysis

Categorical and continuous variables were compared with X^2 test and Student's t-test, respectively. The survival of patients with missed cancer was compared with patients without prior EGD. Kaplan–Meier analysis was performed for this purpose. SPSS 24.0 software (SPSS Software, SPSS Inc., Chicago, IL) was used for all statistical analyses. Statistical significance was considered as $p < 0.05$.

3. Results

A total of 212 GC cases were identified during the 5-year study period; 25 patients were excluded, leaving a total of 187 patients included for the analysis (Fig. 1). Seventeen out of 187 patients had a prior negative EGD within 3 years of the diagnosis of GC (miss rate: 9.1%). Demographic and clinical data of patients with and without missed GC showed no difference (Table 1).

Twelve out of 17 missed GCs had some abnormality in the prior EGD and in 6 of them, biopsies were taken (only in 3 cases more than 4 biopsy samples were taken). In 5 patients, the prior EGD showed gastric ulcers that were misdiagnosed as benign ulcers. In patients without abnormal findings, no biopsies were obtained. Endoscopy findings of patients with missed GC are shown in Table 2.

The median delay from the prior EGD to cancer diagnosis was 28 weeks (range, 8–152 weeks). Ninety-one (48.6%) patients died in the first year and a total of 137 (73.3%) patients had died at the end of the study. The median survival time was 628 days (95% confidence interval [CI], 214–852 days) and 387 days (95% CI, 317–561 days), for patients with and without missed GC, respectively. Survival was no different between the groups ($p = 0.64$) (Fig. 2).

All EGD (previous and diagnostic) were performed by different but fully trained gastroenterologists, by using videoendoscopes and sedation. The following quality indicators were adequately met: EGDs performed by a fully trained endoscopist (100%), complete examination (100%), and adequate description/location of peptic gastric ulcer (100%). Endoscopy time was not measured, and image documentation was inadequate in all patients. Quality indicators in prior EGDs are shown in Table 3.

Table 1
Characteristics of all patients and the groups of patients with or without a prior EGD in the 3 years before a diagnosis of GC.

	Total		Patients without prior EGD		Patients with prior EGD		p
	n	%	n	%	n	%	
Patients (n)	187	100	170	100	17	100	
Mean age (years)	72.1	–	72.1	–	71.9	–	ns
Gender							
Female	78	42%	70	41%	8	47%	ns
Male	109	58%	100	59%	9	53%	
Familial history of GC							
No	66	35%	60	35%	6	35%	ns
Yes	13	7%	11	7%	2	12%	
None reported	108	58%	99	58%	9	53%	
H. pylori infection							
Negative	177	95%	160	94%	17	100%	ns
Positive	10	5%	10	6%	0	0%	
Alarm symptoms							
No	24	13%	22	13%	2	12%	ns
Yes	163	87%	148	87%	15	88%	
Prior gastrectomy							
No	179	96%	163	96%	16	94%	ns
Yes[a]	8	4%	7	4%	1	6%	
Location							
Proximal (fundus/cardia)	31	17%	30	18%	1	6%	ns
Medial (corpus)	57	31%	48	28%	9	53%	0.01
Distal (antrum/angular incisura)	81	43%	76	45%	5	29%	ns
Stump	8	4%	7	4%	1	6%	ns
Multifocal (≥2 parts)	10	5%	9	5%	1	6%	ns
Histology							
Intestinal	110	59%	102	60%	8	47%	ns
Diffuse	49	26%	43	25%	6	35%	ns
Mixed	11	5.9%	9	5%	2	12%	ns
Undifferentiated	1	0.5%	1	1%	0	0%	ns
None reported	16	8.6%	15	9%	1	6%	
T[b] (grouped)							
0/1	21	11%	18	11%	3	18%	ns
2/3	87	46.5%	79	46%	8	47%	ns
4	72	38.5%	66	39%	6	35%	ns
None reported	7	4%	7	4%	0	0%	
TNM[b] (grouped)							
0/1	31	17%	27	16%	4	23%	ns
2/3	51	27%	48	28%	3	18%	ns
4	97	52%	87	51%	10	59%	ns
None reported	8	4%	8	5%	0	0%	
Treatment							
Curative	68	36%	61	36%	7	41%	ns
Palliative	82	44%	76	45%	6	35%	ns
Comfort	37	20%	33	19%	4	24%	ns
Performance status (grouped)							
0/1	145	77%	132	78%	13	76%	ns
2	18	10%	15	9%	3	18%	ns
3/4	24	13%	23	13%	1	6%	ns

EGD: Esophagogastroduodenoscopy. GC: Gastric cancer; ns: no significant.
[a] Operated on for peptic ulcer.
[b] Tumor node metastasis (TNM) staging of gastric cancer (American Joint Committee on Cancer (AJCC), 7th edition) [9].

4. Discussion

This is the first study that evaluates the missed rate of GC in Spain in a cohort of patients with symptoms and shows that it is one of the lowest reported in Western countries. Most importantly, a significant proportion of patients with GC were misdiagnosed at the first endoscopy because of a variety of errors made by the endoscopists, including misinterpretation of some findings, detecting an abnormality but not taking a biopsy, taking an insufficient number of biopsies, and lack of follow-up.

Missed GC is a worldwide problem and occurs in both screening and diagnostic endoscopies [8,10]. The definition of missed cancers is variable and includes different periods, usually from 1 to 3 years after a negative EGD. Assuming that the doubling time for mucosal cancers is 2–3 years [7], upper gastrointestinal cancers diagnosed within 2–3 years after a normal endoscopy may be associated with an unnoticed lesion at the time of endoscopy ("possibly missed"), whereas a cancer diagnosed within a year after a normal endoscopy would almost certainly have been present as a macroscopic lesion at the time of the initial endoscopy. In the meta-analysis of Menon and Trudgill, failure to diagnose or missing an upper gastrointestinal cancer at endoscopy occurred in 6.4% (3.2%–14%) of cases within 1 year and 11.3% (4.6%–21.6%) of cases up to 3 years before diagnosis [11].

Table 2
Characteristics of prior EGD and diagnostic EGD.

	Prior EGD					Diagnostic EGD						
ID	Indication	Findings	Biopsies	Histology	Sedation	Indication	Location	Findings	Histology	TNM	Stage	Delay: weeks (year)
1	Epigastralgia, anemia	Normal	0	–	Propofol	+CT suspicious	Medial	Proliferative lesion	Diffuse	T3N1M1	IV	7.7 (<1 year)
2	Dysphagia	Normal	0	–	Propofol	+WL	Medial	Nodule	Mixed	T4N1M1	IV	10.6 (<1 year)
3	Dysphagia	Hypertrophic folds	5	Gastritis	Propofol	+WL, CT suspicious	Proximal	Ulcerative lesion	Intestinal	T3N0M1	IV	13 (<1 year)
4	UGIB	Peptic ulcer	0	–	Midazolam	+WL, CT suspicious	Distal	Peptic ulcer	Diffuse	T3N1M1	IV	16 (<1 year)
5	Epigastralgia, WL	Hypertrophic folds	6	Gastritis	Midazolam	+CT suspicious	Multifocal	Hypertrophic folds	Diffuse	T4N2M0	III	17.3 (<1 year)
6	Epigastralgia, WL	Erythema/erosion	3	Gastritis	Propofol	+UGIB	Medial	Peptic ulcer	Diffuse	T4N0M1	IV	18.7 (<1 year)
7	UGIB	Peptic ulcer	0	–	Midazolam	UGIB again	Medial	Proliferative lesion	Intestinal	T4N1M1	IV	25.3 (<1 year)
8	UGIB	Peptic ulcer	0	–	Propofol	UGIB again	Distal	Ulcerative lesion	Intestinal	T4N0M1	IV	26.1 (<1 year)
9	UGIB	Peptic ulcer	0	–	Propofol	Control	Medial	Peptic ulcer	Diffuse	T3N0M0	II	28.1 (<1 year)
10	Epigastralgia, WL	Erythema/erosion	3	IM	Midazolam	+UGIB	Distal	Peptic ulcer	Diffuse	TisN0M0	0	28.7 (<1 year)
11	Vomits	Atrophy	0	–	Propofol	Anemia, CT suspicious	Medial	Proliferative lesion	Intestinal	T4N2M1	IV	35.6 (<1 year)
12	Epigastralgia, WL	Hypertrophic folds	0	–	Propofol	+CT suspicious	Stump	Hypertrophic folds	Intestinal	T1N0M0	I	38.1 (<1 year)
13	Epigastralgia, vomits	Normal	0	–	Propofol	+WL	Medial	Proliferative lesion	Intestinal	T3N3M1	IV	42 (<1 year)
14	Epigastralgia	Hypertrophic folds	4	Gastritis	Propofol	+WL, CT suspicious	Medial	Hypertrophic folds	Diffuse	T4N1M1	IV	92 (<2 years)
15	Epigastralgia	Peptic ulcer	2	IM	Propofol	+Anemia, vomits	Distal	Retractile changes	Intestinal	T2N0M0	I	102.9 (<2 years)
16	Anemia	Normal	0	–	Propofol	+WL	Medial	Proliferative lesion	Mixed	T2N0M0	II	106.4 (<3 years)
17	Epigastralgia	Normal	0	–	Midazolam	Epigastralgia	Distal	Peptic ulcer	Intestinal	TisN0M0	0	151.7 (<3 years)

UGIB: Upper gastrointestinal bleeding (melena or hematemesis); CT: computerized tomography; WL: weight loss; IM: intestinal metaplasia; (+): additional symptoms.

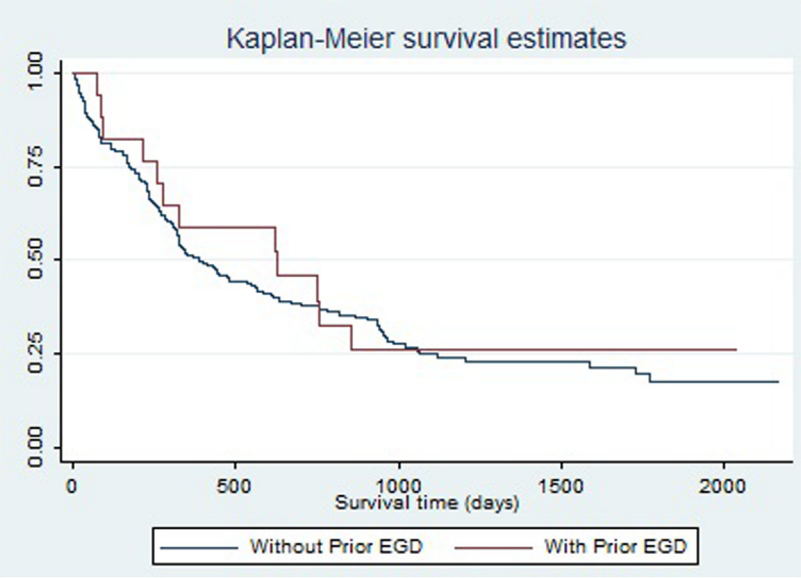

Fig. 2. Survival of GC patients with (missed) and without (non-missed) prior EGD. EGD: esophagogastroduodenoscopy.

Table 3
Quality indicator recommendations and their evaluation at prior EGD.

Intraprocedural quality indicators	ASGE	ESGE	BSG/AUGIS	Prior EGD(n = 17)
Fully trained endoscopist	–	–	100%	17 (100%)
Time recording of endoscopy	–	≥90%	>90%	0/17 (0%)
Complete examination	>98%	–	100%	17 (100%)
Adequate description/location of peptic gastric ulcer (Forrest classification)	>98%	≥95%	–	5/5 (100%)
• Biopsies taken	>80%	–	>90%	1/5 (20%)
• *H. pylori* study	>98%	–	>90%	1/5 (20%)
Biopsies of identified lesions	–	–	>90%	6/12 (50%)
Biopsies if atrophy or intestinal metaplasia was suspected (Sydney protocol)	–	≥90%	>90%	0/1 (0%)
Biopsies if iron deficiency anemia was studied	–	–	>90%	0/2 (0%)
Image documentation	–	–	–	10/17 (59%)
Adequate image documentation	–	≥90%	>90%	0/17 (0%)
Image documentation of detected lesions	100%	–	>90%	9/12 (75%)

ASGE: American Society of Gastrointestinal Endoscopy [21].
ESGE: European Society of Gastrointestinal Endoscopy [22].
BSG/AUGIS: British Society of Gastroenterology and Association of Upper Gastrointestinal Surgeons of Great Britain [23].

The design of the previous studies does not seem to affect the ratio of missed cancers, as shown in the meta-analysis of Pimenta-Melo et al. [10] This meta-analysis included 5 studies with patients who underwent a negative EGD and were followed over time [15,18,26–28] and 9 studies with patients with GC that evaluated how many had a recent negative EGD [12–14,16,17,19,20,29,30]. The pooled missed GC proportion was 9.4% (10% in the first group of studies and 8.3% in the second one). All the studies except one were retrospective.

Countries in East Asia have a high incidence of GC (>20 cases/100,000; incidence standardized by age). Screening programs, especially in Japan, have increased the cases at early stages in up to 90% and, consequently, have achieved an improvement in survival [8,31]. Despite the high expertise of Japanese endoscopists in the detection of early cancer, the presence of very subtle changes in the mucosa might explain why the reported miss rate in Japan is surprisingly higher (up to 25%) than in the West [32].

On the other hand, in countries with low and intermediate risk, such as Spain, there are no screening programs and EGD is performed only in symptomatic patients, who are likely to have more advanced cancer [3,4]. Vradelis et al. reported that more than 90% of patients with GC had alarm symptoms at diagnosis. In our series, all the patients had symptoms at the time of the prior endoscopy, and this should have alerted the endoscopist about the risk of unseen missed lesion. Alarm symptoms have been associated with an increased risk of missing cancer at endoscopy. Fortunately, and similar to other studies, the delay in the diagnosis of GC did not have a negative impact on the final stage of the tumor (with a global 11% of early GC detected and 18% detected in the patients with prior negative EGD) nor in the survival [14,17,18]. By contrast, a recent study conducted in Taiwan outside a screening program showed that a prior EGD improved the 5-year mortality [33]. However, this study included patients with known high-risk lesions who were followed up, whereas patients with peptic ulcer or pre-neoplastic lesions were excluded in our study.

Pre-malignant lesions and early cancers can be very subtle, and endoscopists should be familiar with their endoscopic appearance [34]. Furthermore, a complete observation of the gastric mucosa must be done. To improve the detection of lesions, specialized training in the endoscopic appearance of early lesions, use of mucolytic and defoaming agent before the exploration, and the use of proper sedation, which provide the ideal conditions for endoscopists, were proposed [34,35]. Another proposed measure is to identify patients at high risk of gastric cancer before endoscopy. The factors that increase the risk of GC have been widely studied and are related to age, male sex, ethnic group, active or past infection with *H. pylori*, tobacco or alcohol consumption, type of diet (cured foods with high salt content), and family history of GC [5,8,36,37]. In these high-

risk groups, the performance of more specialized endoscopies (i.e., use of chromoendoscopy) could improve the identification of early, subtle lesions [37,38].

Technical limitations in endoscopy technique, lesion recognition, and sampling error are possible explanations for a missed GC. In the studies that reported endoscopic findings, at least half of the patients with a missed upper gastrointestinal cancer had a described abnormality at the site of the cancer that was either not biopsied or inadequately biopsied [15,39]. An adequate number of biopsies is also a crucial factor. An insufficient number (<6) has been reported as a predictive factor for missing a GC [16], whereas when at least 5 biopsy samples are taken, the accuracy for diagnosing GC is about 97% [40]. In our study, 71% of patients had an abnormality that was described at the prior endoscopy, but biopsies were only obtained from half of the patients, and only in one patient 6 were performed. In patients with a gastric ulcer, it is surprising that malignancy was not suspected in 4 of 5 cases because neither biopsies nor follow-up were performed [21]. If we had considered these cases as misdiagnosed instead of missed neoplastic lesions, the rate of real missed GC in our series would have been lower (6.4%).

Another factor associated with diagnostic errors is the location of the tumor. In our series, location in the medial stomach was statistically associated with a higher risk of missing a lesion. Other reported factors, such as age and sex, were not associated with more missed cancers.

Quality indicators were developed to minimize diagnostic errors. In this study, we observed a good compliance in several quality indicators: performance of endoscopies by fully trained endoscopists (all of them Gastroenterologists) and complete examination and adequate description and location of a peptic ulcer; however, we detected areas for improvement such as time recording, adequate image documentation, adequate protocol of biopsies, and follow-up of a gastric ulcer (which is recommended to be performed within 6–8 weeks) [21–23,25]. The appropriate time of EGD has been shown to improve the detection of gastric lesions, including early GC [41,42]. The adequate systematic image documentation ensures a complete exam and review of the images by other endoscopists can improve the detection of premalignant and early lesions [34,43–45].

The strength of this study is that patients came from a small geographic area and were taken care of in three community hospitals. Therefore, there was a very low risk of having missed a prior endoscopy, because they were all performed in these hospitals.

Despite the fact that patients were from a small geographical area, one limitation is that the number of missed GCs was much lower than GCs diagnosed in the first endoscopy, and the results of the statistical analysis should be interpreted with caution. Another limitation is the retrospective design, which precluded the collection of data such as proton pump inhibitor (PPI) use, duration of the endoscopy, or the quality of gastric mucosa cleaning, among others.

5. Conclusion

The proportion of missed GC in an EGD in Spain is not uncommon but is one of the lowest reported in a Western country. On the basis of our results, the endoscopist is an important factor for missed cancer (lack of lesion recognition and sampling error), and efforts must be made to achieve an adequate proficiency. Compliance with quality indicators, including a more rigorous protocol of biopsies and repeat endoscopy must be implemented to reduce the number of missed GC at the initial endoscopy.

Conflict of interest
None declared.

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