

Missed diagnosis of early gastric cancer or high-grade intraepithelial neoplasia

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Abstract

AIM: To investigate the causes of missed diagnosis of early gastric cancer (EGC) or high-grade intraepithelial neoplasia (HGIN) in Chongqing, China.

METHODS: The present study summarizes 103 cases of EGC/HGIN detected by esophagogastroduodenoscopy (EGD) and pathological analysis from January 2010 to December 2011. Dimethyl silicone oil was administered orally 15 min before the EGD procedures. The stomach was cleaned by repeated washing with saline when the gastroscope entered the stomach cavity. Suspected EGC lesions were subject to conventional biopsy sampling and pathological examinations. The correlation between lesion locations, endoscopic morphology of cancerous sites, training level of the examiners, pathological biopsies, and missed diagnosis was analyzed.

RESULTS: Twenty-three cases were missed among the 103 cases (22.23%) of EGC/HGIN. The rate of missed EGC in the gastroesophageal junction (8/19, 42.1%) was significantly higher than at other sites (15/84, 17.86%) ($\chi^2 = 5.253$, $P = 0.022$). In contrast, the rate of missed EGC in the lower stomach body (2/14, 14.29%) was lower than at other sites (21/89,

23.6%), but there were no significant differences ($\chi^2 = 0.289$, $P = 0.591$). The rate of missed EGC in the gastric antrum (5/33, 15.15%) was lower than at other sites (18/70, 25.71%), but there were no significant differences ($\chi^2 = 1.443$, $P = 0.230$). Endoscopists from less prestigious hospitals were more prone to not diagnosing EGC than those from more prestigious hospitals ($\chi^2 = 4.261$, $P = 0.039$). When the number of biopsies was < 4 , the rate of missed diagnosis was higher (20/23, 89.96%) than for when there were > 4 biopsies (3/23, 13.04%) ($P < 0.001$). In addition, there was no significant difference in the rate of missed diagnosis in patients with 1-3 biopsy specimens ($\chi^2 = 0.141$, $P = 0.932$).

CONCLUSION: Endoscopists should have a clear understanding of the anatomical characteristics of the esophagus/stomach, and endoscopic identification of early lesions increases with the number of biopsies.

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Key words: Missed diagnosis; Early gastric cancer; High-grade intraepithelial neoplasia; Endoscopic diagnosis; Biopsies

Core tip: Early gastric cancer (EGC) detection rate in China is much lower than that in Japan, where $> 80\%$ of EGC is detected. How to avoid missed diagnosis of EGC is most important for digestive endoscopy practice. We found that there were many influencing factors for missed diagnosis of EGC. The most critical issue for endoscopists to avoid missed diagnosis is being cautious about each individual patient.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignant carcinomas, which is highly prevalent worldwide. There were 989 600 estimated new cases and 738 000 deaths in 2008, and > 70% of new cases and deaths occurred in developing countries^[1-5]. Although the incidence of GC has been declining in recent years, China still has the most GC patients in the world. Recent statistics show that > 400 000 new cases of GC are confirmed in China annually^[6-8]. The prognosis of advanced GC is poor and its 5-year survival rate is only 20%-40%, but there could be a 5-year survival rate of 90% for early gastric cancer (EGC) after surgical treatment^[9]. Therefore, timely and accurate diagnosis is important for the treatment and prognosis of patients with GC. However, detection rate of EGC in China is generally about 2%-5%. Although at some hospitals in Shanghai, the detection rate of EGC has increased to 20%-28% in recent years, the detection rate is still significantly lower than that in Japan or South Korea^[10,11]. Therefore, it is imperative for endoscopists to make efforts to improve the detection rate of EGC and reduce missed diagnosis in China^[12]. Our study summarizes the missed cases among 103 patients with EGC or high-grade intraepithelial neoplasia (HGIN) admitted to our hospital from 2010 to 2011, and explored the causes of missed diagnosis.

MATERIALS AND METHODS

General information

From January 2010 to December 2010, gastroscopic examinations were performed on 21 500 patients in Xin Qiao Hospital, Chongqing, China and 245 of these were diagnosed with GC. EGC/ HGIN accounted for 17.56% (43/245) of all the cases of GC. From January to December 2011, gastroscopic examinations were performed on 23 000 patients and 230 were found to have GC, and 26.08% (60/230) of them had EGC/HGIN. There were 69 men and 34 women, aged 44-79 years, with an average age of 60.2 years.

Examination methods

In this study, all cases were examined by gastroscopy (Olympus H260 and PENTAX EPK-i-san, Japan). The date of examination and the results, along with the attending doctor and hospital, were recorded. Dimethyl silicone oil was administered orally, 15 min before the esophagogastroduodenoscopy procedures. The stomach was cleaned by repeated washing with saline, when the gastroscope entered the stomach cavity. Suspected EGC lesions were subject to conventional biopsy sampling and pathological examination. The shape and location of the lesions, as well as the extent and site of the biopsies were recorded. Endoscopic diagnosis was performed in accordance with the Paris endoscopic classification of superficial neoplastic lesions^[13]. Pathological diagnosis of EGC/HGIN followed the 2010 version of the World Health Organization classification of tumors of the digestive system^[14].

Missed diagnosis was defined as follows. Patients who were previously diagnosed with other diseases (*e.g.*, gastric polyps or chronic gastritis) at two examinations at < 3 mo apart, and were later confirmed to have EGC/HGIN.

Statistical analysis

Data analysis was conducted using SPSS 20.0 software (Chicago, IL, United States). Comparison between the groups was performed by using χ^2 test or Fisher's exact probability test and $P < 0.05$ was considered statistically significant.

RESULTS

Different lesion locations correlated with different rates of missed diagnosis of EGC/HGIN

There were 23 cases of EGC/HGIN that were not found by endoscopy but were diagnosed later by pathological examination, so the overall rate of missed EGC/HGIN was 22.23% (23/103) (Table 1). In detail, 42.1% (8/19) of cases of EGC/HGIN that occurred in the gastroesophageal junction were missed, and the rate was higher than for other parts of the stomach (15/84, 17.86%; $\chi^2 = 5.253$, $P = 0.022$). The rate of missed EGC in the lower stomach body (2/14, 14.29%) was lower than at other sites (21/89, 23.60%), but there were no significant differences ($\chi^2 = 0.289$, $P = 0.591$). The rate of missed EGC in the gastric antrum (5/33, 15.15%) was also lower than at other sites (18/70, 25.71%), but there were no significant differences ($\chi^2 = 1.443$, $P = 0.230$).

Endoscopists from hospitals of different standing had different rates of missed diagnosis

Among the 23 missed cases of EGC/HGIN, 15 were found to have no abnormalities or were diagnosed with other diseases (*e.g.*, gastric polyps or chronic gastritis) by endoscopy in the less prestigious hospitals (15/23, 65.21%), but were later diagnosed with EGC/HGIN in our hospital (a more prestigious hospital). The other eight cases (8/23, 34.78%) were initially diagnosed with other diseases by endoscopy physicians in our hospital and then with EGC/HGIN after further examinations. The rate of missed diagnosis of EGC/HGIN by endoscopists from less prestigious hospitals was higher than that from more prestigious hospitals ($\chi^2 = 4.261$, $P = 0.039$) (Table 2).

Endoscopic appearance of cancerous lesions affected missed diagnosis of EGC/HGIN

The rate of missed diagnosis of 0-IIc type lesions was 91.3% (21/23), which was higher than that for 0-I (1/23, 4.35%) or 0-IIb (1/23, 4.35%) lesions. However, one 0-IIb lesion in the lesser curvature was missed. At the first gastroscopy examination, no cancerous lesions were found and the patient was treated for gastritis for 1 mo but the symptoms did not improve. The second gastroscopic examination was performed at the request of the

Table 1 Missed diagnosis of early gastric cancer or high-grade intraepithelial neoplasia in different parts of the stomach *n* (%)

| Locations | Total EGC/HGIN | Missed cases |
|---------------------------|----------------|------------------------|
| Gastroesophageal junction | 19 | 8 (42.10) ^a |
| Upper stomach body | 12 | 2 (16.67) |
| Middle stomach body | 11 | 3 (27.27) |
| Lower stomach body | 14 | 2 (14.29) ^b |
| Antrum of stomach | 33 | 5 (15.15) ^b |
| Gastric angle | 14 | 3 (21.42) |
| Total | 103 | 23 (22.33) |

^a*P* < 0.05 *vs* non-missed diagnosis cases; ^bNo statistical differences. EGC: Early gastric cancer; HGIN: High-grade intraepithelial neoplasia.

Table 2 Early gastric cancer or high-grade intraepithelial neoplasia missed by endoscopists at our and other hospitals

| Lesion locations | Other hospitals | Our hospital |
|---------------------------|-----------------|--------------|
| Gastroesophageal junction | 7 | 1 |
| Upper stomach body | 1 | 1 |
| Middle stomach body | 2 | 1 |
| Lower stomach body | 1 | 1 |
| Antrum of stomach | 2 | 3 |
| Gastric angle | 2 | 1 |
| Total | 15 | 8 |

Table 3 Number of biopsies and missed diagnosis *n* (%)

| Biopsies | Missed cases |
|----------|--------------|
| 1 | 7 (30.43) |
| 2 | 7 (30.43) |
| 3 | 6 (26.09) |
| ≥ 4 | 3 (13.64) |
| Total | 23 (100.00) |

patient's family, and flaky red regions were observed in the middle of the gastric body near the lesser curvature. It was further confirmed as intramucosal differentiated-type GC by pathological diagnosis after endoscopic submucosal dissection.

More biopsies resulted in less missed diagnosis

There were 20 patients in whom diagnosis was missed from 1-3 biopsy specimens. The rate of missed diagnosis was 86.96% (20/23). There were three patients in whom diagnosis was missed with four biopsy specimens. The rate of missed diagnosis was 13.04% (3/23). When the number of biopsies was < 4, the rate of missed diagnosis (20/23, 86.96%) was higher than for > 4 biopsies (3/23, 13.04%) (*P* < 0.001). In addition, there was no significant difference in the rate of missed diagnosis in patients with 1, 2 or 3 biopsy specimens ($\chi^2 = 0.141$, *P* = 0.932) (Table 3).

DISCUSSION

The incidence of GC is about 30/100 000 in East Asian countries including China and Japan^[1]. In some regions

of China, the incidence even exceeds 100/100 000^[15,16]. Every year, mass screening in Japan shows the presence of GC in a low proportion of patients receiving gastroscopic examination. It has been reported that in some Japanese hospitals that the diagnosed cases of GC account for only approximately 0.4% of the gastroscopy examinations each year^[17], but the incidence of GC was 1%-1.2% in our endoscopy center, which was significantly higher than that in Japan. In addition, although there are no accurate statistics for EGC detection rate, it is believed that the rate in China is much lower than that in Japan, where > 80% of EGC is detected^[17]. Many factors contribute to the low detection rate of EGC in China, but how to avoid missed diagnosis of EGC is important for digestive endoscopy practice.

We found that lesion location, training level of doctors (doctors from less prestigious hospitals and fewer years of endoscopy experience are considered to have a low level of training), lesion morphology, and the number of biopsies can affect the diagnosis when EGC is not identified. Previous studies have shown that lesion location has a significant effect on EGC missed diagnosis. Hosokawa *et al.*^[18-20] have conducted a survey in Fukui Hospital, where 562 cases of GC were diagnosed from 51 411 (1.05%) gastroscopic examinations, and 188 cases were confirmed as GC within the next 3 years, with an overall missed diagnosis rate of 25.8%. They have also found that doctors with < 10 years experience as an upper gastrointestinal endoscopist missed 32.4% of GC cases, but the missed diagnosis rate was only 19.5% when doctors with > 10 years of experience conducted the examination (*P* < 0.01).

Importantly, EGC in the gastric cardia or body, especially at the lesser curvature or posterior wall, is usually overlooked^[18,19]. Consistent with this, we found that the rate of missed EGC in the gastroesophageal junction near the stomach side was significantly higher than at other sites. Due to the anatomical structure of the cardia, cancerous lesions in these parts are often difficult to observe when the endoscope is withdrawn or reversed. This requires that the endoscopists should carefully investigate the morphological changes in the gastric fundus near the cardia. On one hand, we should not withdraw the gastro-scope too quickly. On the other hand, to avoid the shield of scope itself, it is necessary to observe from both sides of the scope when it is reversed.

Additionally, we found that the proportion of EGC occurring in the gastroesophageal junction was higher than that previously reported. This may have been due to the increased incidence of GC at this site, which needs further large epidemiological investigations. Compared to other sites, the gastric antrum is easy to expose and the rate of missed diagnosis was lower at this site. The rate of missed diagnosis in the gastric antrum was still approximately 15%, therefore, every part of the stomach should be fully and carefully investigated. We also noticed that there was a significant difference in missed diagnosis of EGC between doctors with different training levels in endoscopy, suggesting that the standardization

of endoscopy records and long-term cognitive training for EGC are crucial. The main cause of missed diagnosis of EGC in many primary hospitals is the inadequate knowledge and cognitive ability^[20]. For example, in our study there were several cases of EGC that were misdiagnosed as gastric erosion. Thus, it is urgent for physicians to strengthen their endoscopic training for diagnosis of EGC. Endoscopic appearance also has a significant effect on EGC diagnosis. Compared to the protruding lesions, the depressed lesions were more prone to be missed. This may have been due to the high proportion of depressed lesions in EGC, because we found that superficially depressed lesions accounted for the vast majority of all cases of EGC. However, the rate of missed diagnosis of EGC 0-IIc lesions (IIc, IIc + IIa, IIa + IIc) was still significantly higher than that of 0-II or 0-III lesions. Although the rate of missed diagnosis of 0-IIb EGC was 100% (1/1) in this study, it still calls for more observation on a larger scale. However, we can conclude that 0-II lesions are more easily missed than 0-I and 0-III lesions. Number of biopsies also affected the rate of missed diagnosis. For cases with ≥ 4 biopsies, the rate of missed diagnosis was significantly lower than for those with < 4 biopsies^[21]. In our study, no patients were subjected to other techniques, such as chromoendoscopy, narrow-band imaging (NBI), magnified endoscopy, and NBI + magnified endoscopy, because these new techniques have not been widely adopted in most hospitals in China. If we use these techniques, the results will be better^[22-25]. In addition, whether targeted biopsy sampling can increase the positive rate of EGC/HGIN requires further research.

In summary, there are many influencing factors for the missed diagnosis of EGC. We agreed with Axon that the most critical issue for endoscopists to avoid missed diagnosis is being cautious about each individual patient^[26].

COMMENTS

Background

Gastric cancer (GC) is one of the most common malignant carcinomas. China has the most GC patients in the world. The prognosis of advanced GC is poor but there could be a 90% 5-year survival rate for early gastric cancer (EGC) after surgical treatment. However, detection rate of EGC in China is very low.

Research frontiers

Research of EGC is a hotspot in digestive diseases at present and how to improve the diagnosis rate of EGC is a key problem. This study aimed to analyze the reasons for missed diagnosis of EGC and provide methods to avoid missed diagnosis. With rapid EGC research and development, more new technology will apply.

Innovations and breakthroughs

Few studies have been carried out focusing on the rate of diagnosis of EGC, due to lack of recognition. The present study was a detailed and systematic study in this field. Furthermore, the study also provides a brighter future in the diagnosis and treatment of EGC, with the development of understanding and new technology.

Applications

This study provides reference data for the diagnosis of EGC. It can be applied to gastroenterologists in hospitals of different rank. There are many influencing factors for missed diagnosis of EGC, but the most critical issue for endoscopists

to avoid missed diagnosis is to be cautious about each individual patient.

Peer review

This is an important analysis of the factors involved in the missed diagnosis of EGC. The authors should use other important techniques, for example: chromoendoscopy, narrow-band imaging (NBI), magnified endoscopy, and NBI + magnified endoscopy. These techniques could change the results.

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