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Modern approaches to diagnosing and preventing malignization of peptic ulcer in the practice of the general practitioner from the perspective of evidence-based medicine.

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Abstract

Background: Peptic ulcer disease (PUD) is a prevalent gastrointestinal disorder that affects millions globally and has the potential to transform into gastric cancer (GC). GC ranks as the fifth most common cancer and is notably lethal. A significant correlation exists between PUD and Helicobacter pylori infection, which disrupts the stomach lining, leading to ulcers that may become malignant if not properly managed.

Methods and Materials: This study employed a systematic analysis and meta-analysis approach, gathering data from multiple medical databases including Medscape, Medline, Scopus, Pubmed, and various gastrointestinal guidelines from regions such as Malaysia, Europe, and the United States. The primary methods involved comparing the risk of malignization between gastric and duodenal ulcers, assessing the sensitivity of different diagnostic methods, and determining optimal prevention strategies.

Results: The findings indicate that gastric ulcers have a higher risk of malignization compared to duodenal ulcers. Diagnostic methods such as endoscopic biopsy demonstrated higher sensitivity for early malignization detection. Screening programs, especially those targeting H. pylori eradication, significantly reduce the incidence and mortality rates associated with gastric cancer.

Conclusion: Early diagnosis and prevention of PUD malignization are vital for improving patient outcomes. Effective strategies include the use of sensitive diagnostic methods and comprehensive screening programs for H. pylori. Lifestyle modifications and vigilant monitoring by healthcare professionals are also crucial in reducing the risk of peptic ulcer malignization and subsequent gastric cancer development.

Keywords: Peptic ulcer disease (PUD), Gastric cancer (GC), Helicobacter pylori (H. pylori), Malignization prevention, Diagnostic methods

List of abbreviation

PUD – peptic ulcer disease

H. pylori –*Helicobacter pylori*

NSAID – non-steroidal anti-inflammatory drugs

CGDU - concomitant gastric and duodenal ulcer

GC - gastric cancer

GI - gastrointestinal

UBT – urea-breath test

FGDS – Fibrogastroduodenoscopy

MDCT - multidetector Computed Tomography

INTRODUCTION

Relevance of the topic

Peptic ulcer diseases are one of the most common gastrointestinal diseases, affecting more than eight million people worldwide. [1] These disorders encompass both gastric and duodenal ulcers. When inadequately treated, gastric ulcers may become cancerous. Epidemiologically, gastric cancer is the fifth most frequent cancer and the third most lethal one. [2] Meanwhile, both gastric cancer and peptic ulcer disease (PUD) show a strong association with the infection of the Gram-negative stomach bacterium *Helicobacter pylori.* Structurally, the stomach's mucous membrane is lined with columnar epithelial cells, secreting digestive enzymes and gastric acid to facilitate the breakdown and assimilation of food. The impermeable lining of these epithelial cells also protects the digestive tract against bacterial infection. However, when the inner lining of the stomach becomes defective following the disparity of digestive juices and the disintegration of the protective barrier of the stomach lining, it gives rise to peptic ulcers. In this respect, *H. pylori* infection is the primary cause of PUD. Chronic inflammation of the stomach's columnar epithelium leads to atrophy, metaplasia, dysplasia, and malignant degeneration, significantly increasing the susceptibility of gastric cancer in patients with PUD.

Early diagnosis of malignization in patients with PUD is crucial in enhancing their survival rates of gastric cancer. Similarly, inhibiting the malignization of peptic ulcer substantially reduces the mortality rate of gastric cancers due to PUD.

Aim of study

This study aims to analyse the association between PUD and gastric cancer, examining the performance of patients with PUD in the prevention or early detection of malignization of peptic ulcer.

Objectives of the study

1. Comparing the risk of malignization between gastric and duodenal ulcers
2. Comparing the sensitivity of different methods for diagnosing the malignization of peptic ulcer
3. Determining the optimal combination of methods for preventing the malignization of PUD

Materials and methods

Methods used in this study included systemic analysis and meta-analysis. Data and information were acquired from various medical databases and internet resources. They included Medscape, Medline, Scopus, Pubmed, and Mayoclinic guidelines of gastrointestinal disease from Malaysia, European Oncology guidelines, and the American gastrointestinal guideline.

Practical significance

This study deliberated the risk of malignization between gastric and duodenal ulcers, potentially predicting the risk of malignization in patients while comparing the sensitivity of various diagnostic methods for the malignization of peptic ulcers. Such a comparison could expedite the diagnosis through the use of methods of higher sensitivity, substantially reducing incidences and prevalence of the development of malignant peptic ulcers.

Chapter 1: Aspects of peptic ulcer malignization

1.1 The association between peptic ulcer diseases and gastric cancer

Peptic ulcer disease is one of the most common gastrointestinal diseases, with a global prevalence of approximately 8.09 million in 2010 [3]. According to the International Agency for Research on Cancer, approximately 20 million incidences of cancer will arise in 2022 [4]. Gastric cancer ranks 5th in global prevalence among malignant neoplasms. This disease is associated with high lethality: in the structure of cancer mortality, gastric cancer occupies the 4th position after lung cancer, colorectal cancer, and liver cancer [5]. In the Russian Federation, cancer was the second leading cause of death in 2022, accounting for approximately 192 deaths per 100 thousand of the country's population [6]. In Malaysia, gastric cancer is the sixth most common cancer among men and the tenth most common cancer among women [7].

Peptic ulcer disease (PUD) is an ailment of defection in the stomach's inner lining with the protective superficial mucosal layer damaged. Complications of PUD encompass gastrointestinal bleeding, perforation, penetration, and malignancy. Once malignized, PUD becomes gastric cancer. In general, both PUD and gastric cancer are in tight association with the infection of *H. pylori*. However, they differ in mechanisms of development. The formation of an ulcer generally involves the breakdown of the protective mucosal barrier. Various aggressive factors, notably *H. pylori* infections and NSAIDs disrupt the stomach's mucosal defence, impairing the gastric epithelial lining's wound-healing processes. Although most peptic ulcers are benign, certain aggressive factors such as *H. pylori* infection, tobacco smoking, and alcohol consumption may sometimes transform them into malignant ones with abnormal cell growth.

In comparison, the development of gastric cancer involves a well-defined cascade of precursors: inflammation, atrophic gastritis, intestinal metaplasia, gastric dysplasia, and, finally, carcinoma. [8] In this respect, the infection of *H. pylori* directly leads to chronic inflammation of the stomach's columnar epithelium. When inadequately treated, the chronic and persistent inflammation of the epithelial lining, in turn, gives rise to atrophic gastritis following the loss of gastric glandular cells and replacement of columnar epithelium by intestinal and fibrous tissues. This replacement is known as intestinal metaplasia. Together, atrophic gastritis and intestinal metaplasia substantially increase the risk of gastric dysplasia and cancer development. Meanwhile, abnormal cells in the stomach's inner lining lead to gastric dysplasia, which is divisible into low- and high-grade dysplasia depending on the cytological and architectural changes.

Despite atrophic gastritis, intestinal metaplasia, and gastric dysplasia are all pre-malignant conditions, only gastric dysplasia could function as the direct precursor because it is the penultimate stage of gastric carcinogenesis. In general, the risk of gastric cancer is positively associated with PUD. Table 1 shows the risk of gastric cancer in the stomach's various pre-malignant conditions. Compared to gastric atrophy, gastric dysplasia shows the highest risk of malignant transformation. [8]

1.2 The association between ulcer characteristics and malignant potential

PUDs include both gastric and duodenal ulcers, which differ in malignant potential. A study showed that patients with gastric ulcers exhibited substantially higher incidence rates than patients with concomitant gastric and duodenal ulcer (CGDU) in both intestinal metaplasia (16.4 vs. 8.3%) and gastric dysplasia (2.7 vs. 0.7%). Patients with gastric ulcers showed a substantially higher prevalence of intestinal metaplasia and gastric dysplasia, indicating a higher risk of developing gastric cancer (i.e., more susceptible) than CGDU patients. [9]

Also, the ulcer's size and location are critical in determining the risk of malignancy transformation. In a study predicting the risk of malignancy transformation based on the size of the ulcer, 111 patients with giant gastric ulcers exceeding 3 cm were investigated over ten years from September 2005 to December 2015, with the patient's median age at 75 years old. [10] Predictors for malignancy included ulcer location, patient's age, and the endoscopist's suspicion during endoscopy. Among the 111 patients, 58.6% (65) had suspicious ulcers, 34.2% (38) carried non-suspicious ulcers, while 7.2% (8) had missing data. Figure 1 shows that giant gastric ulcers had a high malignancy yield of 37.8%, and 30.6% of the 42 malignant giant gastric ulcers were adenocarcinoma. [10]

Meanwhile, Figure 2 shows the distribution of benign and malignant giant gastric ulcers according to the anatomic location. Giant gastric ulcers occurred most frequently on the stomach's body (50.9%) and followed by the antrum (37.1%). Giant gastric ulcers located at the incisura showed the highest risk of malignancy, i.e., 90.5% (4/6), followed by the cardiac region at 60.4% (6/10), the stomach's body at 41.5% (22/53), and the antrum/pre-pyloric area at 23.8% (10/42). [10]

1.3 Classification and staging of peptic ulcer malignization

Most (about 90%) gastric cancers are adenocarcinoma, and they arise from the mucus-producing cells in the gastric mucosa. Based on the anatomic location, gastric adenocarcinoma is divisible into cardiac and non-cardiac. The former emerges from the gastro-oesophageal junction, while the latter arises more commonly from the stomach's lower portion. [2] Other gastric cancers include lymphoma (5%), carcinoid, and stromal, and they are rather rare.

To establish the stage of the disease, TNM system (2018) is introduced, in which the T category denotes the depth of tumor infiltration into the organ wall, N is the lymph node status, and M describes the presence of distant metastases. [11]

T- primary tumor (depth of invasion of the stomach wall)

Tx Primary tumor cannot be evaluated

T0 No evidence of primary tumor

Tis Carcinoma in situ (tumor within the mucosa without invasion of the lamina propria)

T1a Tumor invades the lamina propria or the muscularis mucosa

T1b Tumor invades the submucosal layer

T2 Tumor invades the muscularis propria

T3 Tumor penetrates the subserosa without invasion of the visceral peritoneum or adjacent structures; tumors in this group include tumors with invasion of the gastro-obstetric and gastrohepatic ligaments, the greater and lesser omentum without invasion of the visceral peritoneum

T4 Tumor invades the serous membrane (visceral peritoneum) or adjacent structures

T4a Tumor invades the serous membrane (visceral peritoneum)

T4b Tumor invades the adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, anterior abdominal wall, adrenal gland, kidney

N - lymph nodes affected by metastasis

Nx Regional lymph nodes cannot be evaluated

N0 No metastases in regional lymph nodes

N1 1 to 2 affected lymph nodes

N2 3 to 6 affected lymph nodes

N3 7 or more affected lymph nodes

N3a Metastasis to 7 to 15 regional lymph nodes

N3b Metastasis to 16 or more regional lymph nodes

M - distant metastases

M0 No distant metastases

M1 Presence of distant metastases

Classification of gastric cancer by stage

Stage T-Primary tumor Lymph nodes affected by metastases

Distant metastases

Stage 0 Tis N0 M0

Stage IA T1 N0 M0

Stage IB T2 N0 M0

T1 N1 M0

Stage IIA

T3 N0 M0

T2 N1 M0

T1 N2 M0

Stage IIB

T4a N0 M0

T3 N1 M0

T2 N2 M0

T1 N3 M0

Stage IIIA

T4a N1 M0

T3 N2 M0

T2 N3 M0

Stage IIIB

T4b N0, N1 M0

T4a N2 M0

T3 N3 M0

Stage IIIC T4b N2, N3 M0

T4a N3 M0

Stage IV Any T Any N M1

Chapter 2: Peculiarities of the diagnosis in peptic ulcer malignization

2.1 Physical examination of patients

Patients of PUD usually complain about epigastric pain related to food, abdominal bloating, nausea and vomiting, anorexia, dyspepsia, dysphagia, or hematemesis if PUD is complicated with gastroduodenal bleeding. Since the malignization of peptic ulcer shows no specific symptoms, one should be cautious about significant weight loss, dysphagia, severe nausea, vomiting, or multiple (more than 3) PUD symptoms. These traits might serve as alarming symptoms because they often appear in the malignization of PUD. An analysis of PUD patients (Table 3) revealed a very high specificity in alarming features, i.e., 96% gastrointestinal bleeding, 97.6% body weight loss, 99.8% dysphagia, and 93.8% with at least one alarming feature. [12] However, the sensitivity was relatively low, i.e., 24.4% GI bleeding, 29.3% body weight loss, and 60.1% with at least one alarming feature, especially for dysphagia (14.6%). Patients with upper gastric cancers showed the highest prevalence rate (85.7%) for at least one alarming feature (83.3%), while both weight loss and dysphagia showed the highest rate, i.e., 50%. However, for patients with lower gastric cancers, GI bleeding (36.5%) was the most prevalent alarming feature. [12]

2.2 Laboratory diagnosis of peptic ulcer malignization

The diagnosis of PUD in routine blood and urine tests is generally non-specific. However, for PUDs caused by the infection of *H. pylori*, several diagnostic tests are available, including the urea breath test, serological test, stool antigen test, microbial culture, histological examination and staining, and the rapid urease test from gastric biopsy. Similarly, laboratory screenings for gastric cancer are generally non-specific. Complete blood count tests may reveal anaemia as cancer progresses. Electrolyte panels and liver function tests should also be performed despite their lack of specificity.

Commonly used tumour markers for gastric cancers include CA 12-5, carcinoembryonic antigen (CEA), and cancer-related antigen 19-9 (CA 19-9). Despite a relatively high specificity, the sensitivity of these markers remains uncertain. One study [13] found that CA 12-5 was the least sensitive marker (7.0%) but with high specificity (99.0%), while CEA showed a sensitivity of 22.6% and a specificity of 98.0%, and CA 19-9 exhibited a sensitivity 20.0% and a specificity of 99.0%. In combination, these markers yielded significantly higher sensitivity than when used separately at an acceptable reduction in specificity, with a composite sensitivity and specificity of 65.2% and 84.9%, respectively. [13] However, another study [9] concluded that the sensitivity of CEA, CA12-5, and CA19-9 in the diagnosis of gastric cancer ranged from 4.7–20.8% individually and increased to 40.3% in combination. [14] Fortunately, both studies showed a higher sensitivity when combined with these markers than when used separately.

Conventionally, endoscopic gastric biopsy is the gold standard for diagnosing gastric cancers. A single biopsy generally yields a sensitivity of 70% for diagnosing an existing gastric cancer. Nevertheless, sampling numerous biopsies from suspicious-appearing lesions and smaller, benign-appearing gastric ulcers is necessary for diagnosing patients with a higher risk for gastric cancers. After seven biopsies along the ulcer margin and base, the sensitivity was found to increase to 98%. [15]

Histopathologically, there are several universal schemes used for classifying gastric cancers. Table 3 shows the 1965 Lauren classification of gastric cancers with three main histological subtypes, i.e., intestinal (54%), diffuse (32%), and mixed (15%). The intestinal subtype is distinctive, whereas the diffuse one is poorly differentiated or non-specific. The

mixed subtype consists of at least two other forms of independent histological variants. Meanwhile, the 2010 WHO scheme classifies gastric cancers into five histological patterns: tubular, papillary, mucinous, poorly cohesive (including signet ring cell carcinoma and other forms), and mixed variants (Table 4). A tubular adenocarcinoma typically exhibits unevenly distended, fused, or bifurcating tubules of various sizes, often with intraluminal mucus nuclear and inflammatory debris. In the papillary adenocarcinoma, a central fibrovascular core scaffolds the epithelial projections, whereas the mucinous adenocarcinoma consists of extracellular mucinous pools constituting at least 50% of the tumour volume. Signet ring cell carcinoma and other poorly cohesive carcinomas are often composed of signet ring cells and non-signet ring cells. [16]

2.3 Instrumental diagnosis of peptic ulcer malignization

Instrumental diagnosis of peptic ulcer malignization is more reliable than laboratory screening. The principal technique for instrumentally diagnosing malignization of PUD is the fibrogastroduodenoscopy (FGDS) with biopsy. Since this method could determine the size and location of the malignant ulcer, it thus allows direct visualization of the gastric mucosa to secure tissue samples for biopsy and histopathological evaluation. Based on macroscopic features, the Paris scheme sub-classifies early gastric carcinomas into three forms: 0-I (protruded), 0-II (superficial), and 0-III (excavated), as shown in Figure 3. Type 0 lesions are superficial in appearance and further subdivided into polypoid and non-polypoid. Designated as Paris classification 0-I, polypoid lesions can either be pedunculated (0-Ip), sessile (0-Is), or semi-pedunculated (0-Isp). By contrast, 0-I lesions are usually larger in size than benign polyps, exhibiting a granular or lobulated shape with a rough surface. Non-polypoid lesions can be further subdivided into excavated (0-III) and flat lesions (0-II). Flat lesions can be either slightly elevated (0-IIa), flat (0-IIb), or slightly depressed (0-IIc). [17]

For advanced gastric carcinomas they are sub-classified according to their gross appearance. In this respect, the Borrmann scheme groups the advanced gastric carcinomas into polypoid (type I), fungating growth (type II), ulcerating growth (type III), and diffusely infiltrative growth (type IV), as shown in Figure 4. [18]

In instrumental analysis, the barium swallow demarcates the anomalies of the stomach's lining caused by ulcers, and the occurrence of defining features will enable us to differentiate benign and malignant ulcers. Malignant ulcers show irregular and shallow craters with nodular and angular ulcer mounds. By contrast, benign ulcers exhibit smooth, rounded, deep ulcer craters and smooth ulcer mounds. Also, malignant ulcers do not protrude beyond the gastric contour, whereas benign ulcer craters protrude beyond the gastric contour. Besides, the Carman meniscus sign is usually positive in malignant ulcerated neoplasm. [19]

For the clinical staging of gastric cancers, except for patients with contraindications, the first-line method of diagnosis is usually the MDCT scan. The CT scan is a non-invasive method, and it allows us to assess the local extension of tumour, nodal disease, and metastases. The sensitivity of CT scans for diagnosing advanced gastric cancer is about 65%−90%, with an accuracy of 70%−90% for T staging and 40%−70% for N staging. [20] Table 5 shows the pathologic T stages and MDCT criteria of T staging modified to the latest TNM staging. Focal and eccentric wall thickening exceeding 5 mm is considered malignancy. [21]

Chapter 3: Prevention of peptic ulcer malignization

3.1 Primary prevention

The primary prevention of PUD malignization aims to halt the occurrence of PUD. Risk factors such as *H. pylori* infection, tobacco smoking, high alcohol consumption, and long-term use of NSAIDs have long been known to increase the risk of PUD, and hence they should be stopped or reduced. Cessation of smoking, reduction in the consumption of alcohol, avoidance of the long-term use of NSAIDs, and improvement in obesity are some of the interventions generally practiced in the primary prevention of PUD.

3.2 Secondary prevention

The secondary prevention consists of interventions implemented to prevent complications by early diagnosis and management. Screening programs for detecting the infection of *H. pylori* have been implemented in some Asia countries to improve its eradication. (Table 6). The program shows that screening reduces gastric cancer incidence and mortality rate. Unfortunately, no such screening program is implemented in Western countries. [22]

Gastric cancer screening typically involves contrasting radiography and endoscopy to detect the pre-malignant condition and lesions in the stomach lining, and it allows early detection of cancers. A case-control study was performed in Korea using data from the Korean National Cancer Screening Program for gastric cancer since 2002 because Korea is one of the high-risk areas for gastric cancer. [23] This study reported that Korea showed an overall 21% reduction in gastric cancer mortality upon implementing the nationwide screening program using upper endoscopy or upper gastrointestinal series. Individuals aged 40–74 years who performed upper endoscopy screening also showed reduced mortality. The overall reduction in the death risk of gastric cancer was 47%. However, screening with the UGI series did not show this reduction. [18] Other non-invasive methods for screening gastric cancer include serum pepsinogen test, H. pylori serology, and Trefoil factor 3.

Another crucial component of the secondary prevention of malignization of PUD is through managing diseases that increase the risk of PUD to prevent complications of PUD. In this respect, *H. pylori* infection is the most common cause of PUD. The principal method of eradicating *H. pylori* is a PPI-based triple therapy, which includes a proton pump inhibitor combined with amoxicillin and clarithromycin or a Bismuth-based triple (bismuth+ metronidazole + tetracycline)/quadruple therapy (bismuth + metronidazole + tetracycline + PPI).

Meanwhile, the Epstein–Barr virus also increases the risk of PUD and the development of pre-malignant and malignant gastric ulcers, even though such incidence is uncommon [24]. However, the association between the Epstein-Barr virus and carcinogenesis varies in different countries. [25] In any case, early management of Epstein-Barr virus infection is crucial in PUD patients with negative *H. pylori* infection and/or NSAID use.

Conclusion

An early diagnosis and the prevention of peptic ulcer malignization are crucial in treating and managing patients. An accurate diagnosis allows healthcare professionals to identify the malignization of peptic ulcers, thereby enabling timely intervention and appropriate treatment. Various diagnostic methods, including endoscopy, barium swallow, and biopsy, are commonly employed to confirm malignancy. An early detection of malignization is vital to enhance a patient's survival while reducing the risk of complications.

Preventing the malignization of peptic ulcers is another essential aspect of patient care. It can be achieved through various strategies, notably the eradication of *Helicobacter pylori* infection, a major risk factor for developing peptic ulcers and subsequent malignancy. Lifestyle modifications, such as avoiding smoking and alcohol consumption, maintaining a healthy diet, and managing stress levels, can further contribute to the prevention of peptic ulcer malignization. Finally, healthcare professionals should remain vigilant in monitoring patients with peptic ulcers and be proactive in implementing preventive strategies to ensure optimal patient care.

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Table 1: Gastric cancer risk for pre-malignant stomach.

Pre-malignant mucosa	Annual incidence (%)	5-year cancer incidence (%)
Severe gastric atrophy		10
Mild gastric atrophy		0.7
All grades of gastric atrophy	<0.5	<2
Antral & corpus intestinal metaplasia		10
Antral intestinal metaplasia		5
All grades of intestinal metaplasia	<0.4	4 months to 2-year interval
High-grade dysplasia	6	60–85
Low-grade dysplasia	0.6	0–23

Figure 1. The flow diagram of patients for the giant gastric ulcer cohort.

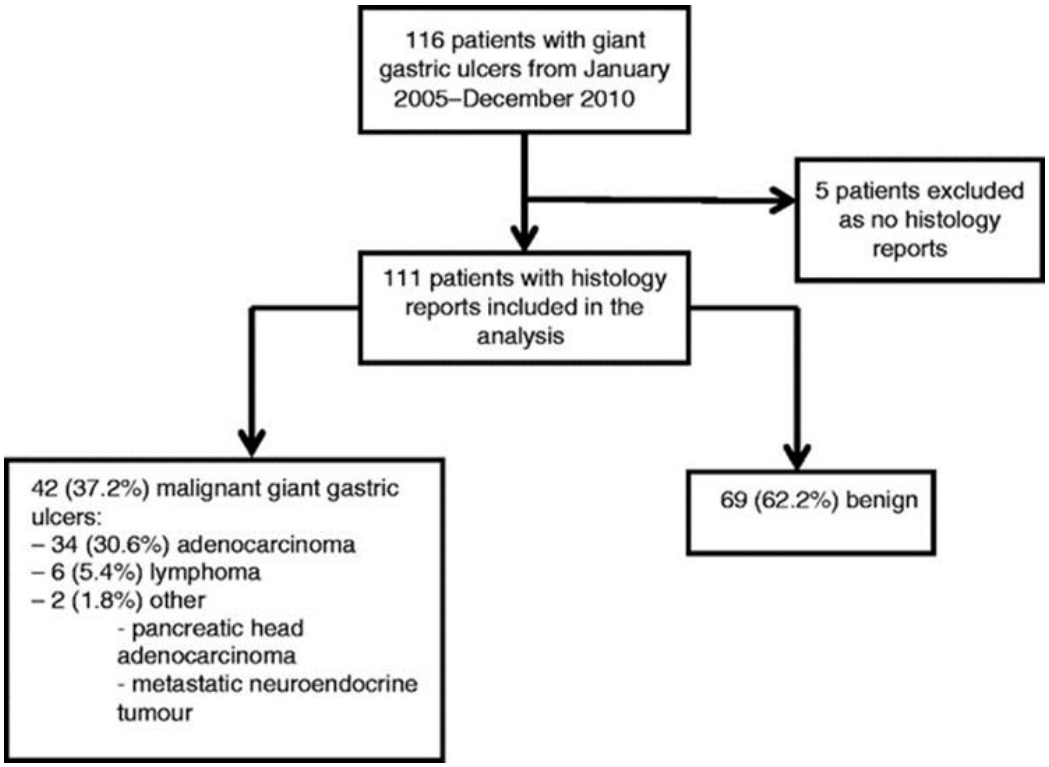


Figure 2. The distribution of the location of benign and malignant giant gastric ulcers.

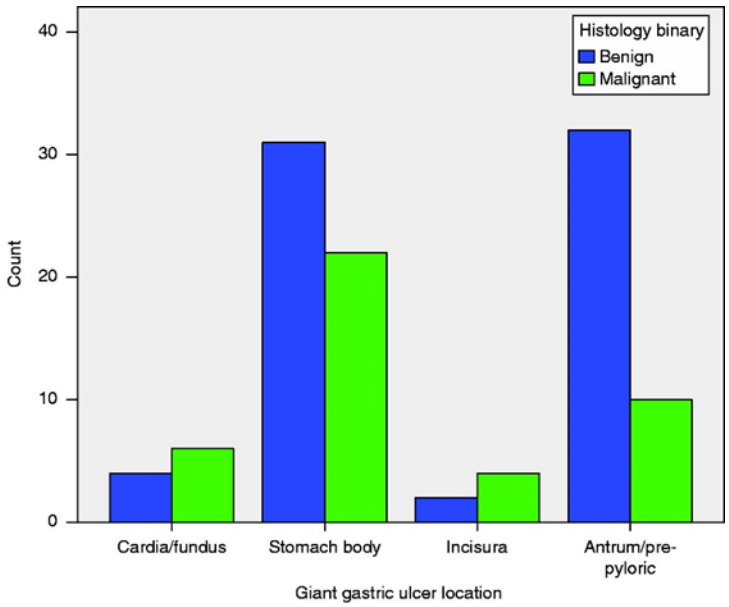


Table 2. The TNM staging in gastric cancer.

T0	No evidence of primary tumour
Tis	The cancer is found only in cells on the epithelium and has yet to spread to any other layers of the stomach.
T1	Tumour has grown through the lining and into the connective tissue
T2	Tumour has grown into the muscle layer of the stomach
T3	Tumour has spread through all the muscle layer and outer lining but not to organs and tissues
T4	Tumour has grown to nearby tissues and organs
T4a	Tumour has grown into the serosa
T4b	Tumour has grown into organs surrounding the stomach
N0	Cancer has not spread to lymph nodes
N1	Cancer has spread to one to two regional lymph nodes
N2	Cancer has spread to three to six regional lymph nodes
N3	Cancer has spread to seven or more regional lymph nodes
N3a	Cancer has spread to seven to 15 regional lymph nodes
N3b	Cancer has spread to 16 or more regional lymph nodes
M0	No metastasis
M1	Metastasis

Table 3. The associations of alarming features and upper gastrointestinal malignancies.

	No. of patients with alarming features	No. of patients with upper GI malignancies and alarming features	No. of patients without alarming features	No. of patients with upper GI malignancy but no alarming features	Sensitivity (%)	Specificity (%)
Gastrointestinal bleeding	173	20	3,753	62	0.24	0.96
Weight loss	115	24	3,811	58	0.29	0.98
Dysphagia	18	12	3,908	70	0.15	0.99
At least one alarming feature	290	50	3,636	32	0.61	0.94

Table 4. The 2010 WHO and the 1965 Lauren classification schemes for gastric adenocarcinoma.

WHO (2010)	Lauren (1965)
Papillary adenocarcinoma Tubular adenocarcinoma Mucinous adenocarcinoma	Intestinal type
Signet-ring cell carcinoma And other poorly cohesive carcinoma	Diffuse type
Mixed carcinoma	Indeterminate type
Adenosquamous carcinoma	
Squamous cell carcinoma	
Hepatoid adenocarcinoma	
Carcinoma with lymphoid stroma	
Choriocarcinoma	
Carcinosarcoma	
Parietal cell carcinoma	
Malignant rhabdoid tumor	
Mucoepidermoid carcinoma	
Paneth cell carcinoma	
Undifferentiated carcinoma	
Mixed adeno-neuroendocrine carcinoma	
Endodermal sinus tumor	
Embryonal carcinoma	
Pure gastric yolk sac tumor	
Oncocytic adenocarcinoma	

Figure 3. Schematic representation of the Paris classification for early gastric cancers.

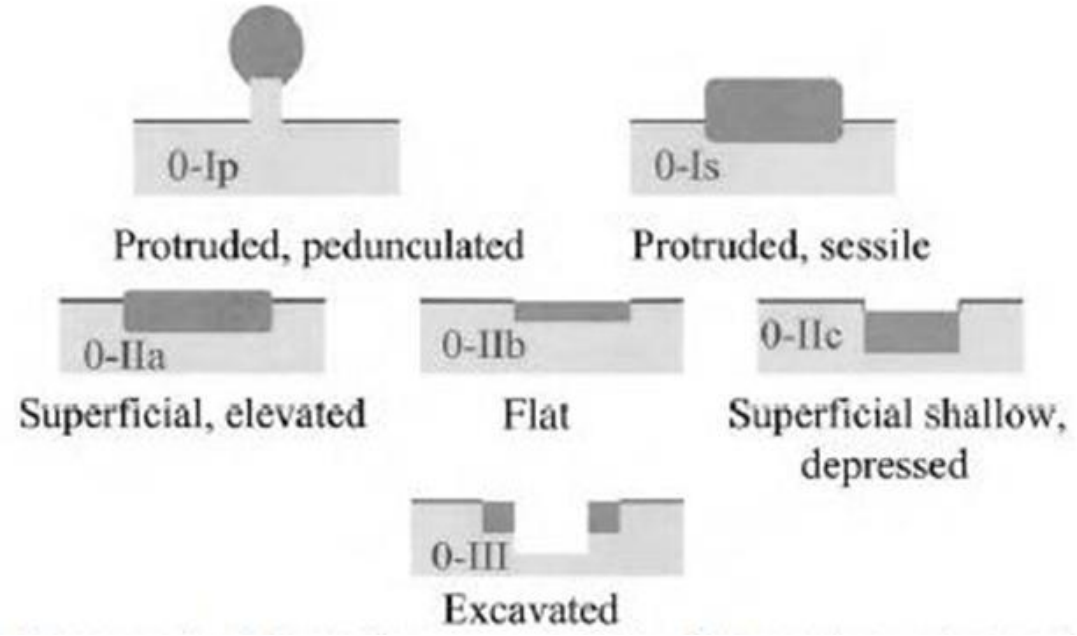


Figure 4. The Borrman classification.

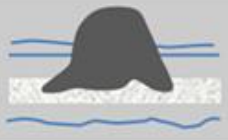
Type I		Polypoid tumors
Type II		Fungating carcinomas
Type III		Ulcerated carcinomas
Type IV		Infiltrating carcinomas

Table 5. Pathologic T stages and MDCT criteria for T stages of gastric cancers.

Pathological T stage	**MDCT criteria**
pT1: tumour invades the lamina propria, muscularis mucosae or submucosa	T1: strong enhancement with focal thickening in the inner and/or middle layer, but the outer layer shows no enhancement; enhancement of the stomach wall only, but the wall is not thickened; wall thickening with intense enhancement of the inner layer and the presence of a hypodense stripe/layer
pT2: tumour invades into the muscularis propria	T2–3: the entire stomach wall is thickened to a variable extent, but there is a regular surface of an outer layer of the gastric wall; the normal appearance of perigastric fat
pT3: tumour invades the subserosa	
pT4a: tumour perforates the serosa	T4a: the entire stomach wall is thickened with homogeneous or inhomogeneous enhancement; the irregular surface of the outer layer of the gastric wall; the presence of micronodules or dense stranding in the perigastric fat
pT4b: tumour invades adjacent structures	The tumour extends into adjacent contiguous organs in addition to wall thickening

Table 6. Screening programs for the infection of H. pylori in Asia.

Country	Screening Age	Beginning of Screening	Screening Interval	Strategy	Expected or Demonstrated Benefits
Japan	20 years	2013	Once	*H. pylori* infection diagnosed at endoscopic screening	6% reduction in GC mortality in 2016
Republic of Korea	40–65 years	2014	Once	Urea breath test (UBT) screening	To reduce the incidence of GC through the eradication of *H. pylori*
China	18 years	2022	Once	Through UBT screening for parents, reach out to children for H. pylori testing.	To prevent the spread of *H. pylori* among family members and thus reduce GC incidence and related costs.
Taiwan	30 years	2004	Every 2 years	UBT screening	53% reduction in GC incidence and 25% reduction in GC mortality.