




REVIEW ARTICLE

One stomach, two subtypes of carcinoma—the differences between distal and proximal gastric cancer

Yuan Zhang [†], Peng-Shan Zhang[†], Ze-Yin Rong and Chen Huang*

Department of Gastrointestinal Surgery, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, P. R. China

*Corresponding author. Department of Gastrointestinal Surgery, Shanghai General Hospital, Shanghai Jiao Tong University, No.100 Haining Road, Hongkou District, Shanghai 200080, P. R. China. Tel: +86-13381758371; Email: richard-hc@sohu.com

[†]These authors contributed equally to this paper.

Abstract

Gastric cancer (GC) is one of the most common malignant tumors of the digestive tract, posing a significant risk to human health. Over the past 10 years, the pathological characteristics and the prognosis of GC have been determined based on the locations of the tumors that were then classified into two types—proximal and distal GC. This review focuses on the differences in epidemiology, etiology, cell source, pathological characteristics, gene expression, molecular markers, manifestations, treatment, prognosis, and prevention between proximal and distal GC to provide guidance and a basis for clinical diagnosis and treatment.

Key words: gastric cancer; epidemiology; pathology; therapeutics; prognosis

Introduction

Although gastric cancer (GC) incidence and mortality have declined significantly over the past 70 years, it is still a leading cause of cancer-related deaths. GC was ranked fifth in morbidity and fourth in mortality in the cancer-prone countries [1] and was second in morbidity and third in mortality in China [2]. GC consists of two subtypes—proximal GC (PGC) and distal GC (DGC)—based on its position-specific features. Herein, we define the tumors on the upper third of the stomach (including gastric cardia cancer and gastric fundus cancer) as PGC and those on the lower third of the stomach as DGC (Figure 1), according to the classification of the Japanese Gastric Cancer Association [3]. Previous studies demonstrated that GC locations are associated with the diverse characteristics of epidemiology, etiology, pathology, and symptomatology. Interestingly, different therapies for PGC and DGC may give rise to varied outcomes. Thus, in this

review, we summarize the differences between PGC and DGC in epidemiology, etiology, cell source, pathological characteristics, gene expression, molecular markers, manifestations, treatment, prognosis, and prevention, with emphasis on the interactions between non-coding RNAs and GC to guide clinical diagnosis and treatment.

Epidemiology

Regional and time distribution

As shown above, GC has high mortality and morbidity, which drop sharply worldwide, and presents various characteristics depending on regional and time distribution. Asia has witnessed a slow decline in carcinogenesis and cancer-related deaths, especially in developing countries. A similar tendency of regional divergence is observed in China: the incidence of GC

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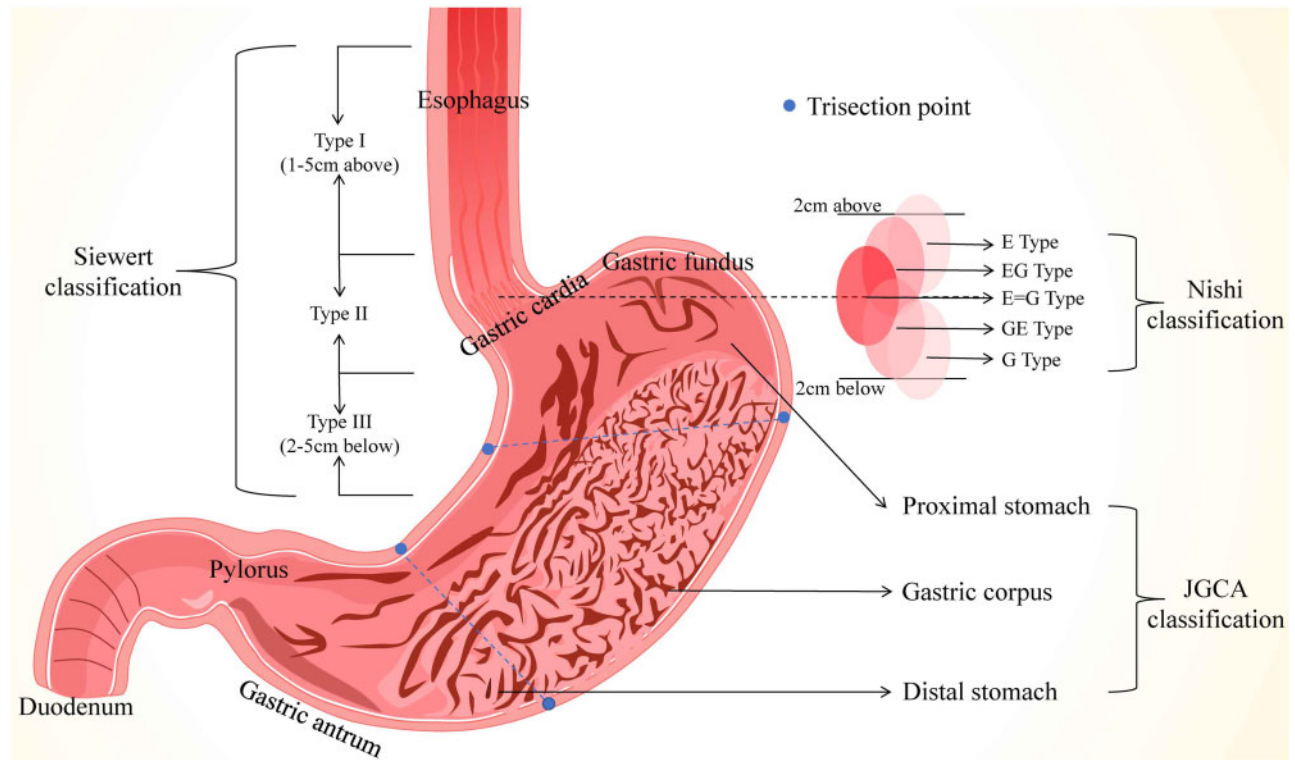


Figure 1. The anatomy and definitions of gastric cancer. (A) Siewert classification classifies tumors into three types: Type I, adenocarcinoma of the distal part of the esophagus—the tumor center is located 1–5 cm above the gastric cardia; Type II, adenocarcinoma of the real cardia—the tumor center is located 1 cm above or 2 cm below the gastric cardia; Type III, adenocarcinoma of the subcardial stomach—the tumor center is located 2–5 cm below the gastric cardia. (B) Nishi's classification defines five types of EGJ cancer featured by diameters of ≤ 40 mm and an epicenter within 2 cm proximal or distal from the EGJ, irrespective of histological type. The “E-G” terms of “E,” “EG,” “E = G,” “GE,” and “G” are used to describe the subtype according to the epicenter location at the rostral and caudal portions of the EGJ. (C) JGCA classification has divided the stomach into three portions: the upper (U), middle (M), and lower (L) parts, by the lines connecting the trisected points on the lesser and greater curvatures, which had been separately identified as the proximal stomach, gastric corpus, and distal stomach.

in eastern China is relatively high, with a downward trend from the east to the west [4]. The prevalence rate in rural areas, especially Gansu, Henan, Hebei, Shanxi, Shandong, and Shaanxi provinces, is high [5].

The predilection site of GC varies significantly with time and space. DGC, with a decreasing trend worldwide, mainly occurs in developing countries, such as countries in East Asia, East Europe, and South America [6]. On the contrary, PGC, with a rising incidence worldwide, is mainly diagnosed in developed countries. PGC morbidity in developed countries (UK and USA) has increased by 5– to 6-fold in the last 30 years. In northwestern Iran, the morbidity of PGC has been increasing for several years, accounting for 43.7% of GC [7].

The distribution of DGC and PGC is similar with respect to time but varies in space. Typically, the morbidity ratio of DGC/PGC was 1.49:1, according to a survey from 1997 to 2017 [4]. Another survey from 1998 to 2008 encompassed 1,090 GC cases in northern Henan, of which 60% comprised gastric cardia and fundus, and 30% were DGC [8]. Hebei Province has witnessed a similar trend, wherein cardia cancer rose from 54.8% to 75.9%, while the antrum-cancer proportion descended from 17.5% to 7.7% from 1993 to 2006 [9]. However, data from Da Bie Mountain pointed out that DGC has a dominant role, accounting for 47.36% of GC cases, i.e. four times the PGC cases [10]. The leading cause for the above distribution difference might originate from the local lifestyle, economic condition, food preference,

and air and water quality. Even without related statistics of other areas, DGC and PGC are specifically featured by space and time distribution.

Population distribution

Age, gender, race, and nationality are essential factors that affect GC population distribution. Based on the relevant statistical data, the peak age of the onset was 40 years. The incidence of GC increases with age and the ratio of male to female patients is about the interval data of 1.5:2.5 vs 1 [11].

GC in various positions showed similar distribution characteristics of the population. Black males with low social status and income comprised the population susceptible to DGC [6]; hence, DGC patients are much younger ($P = 0.046$) [12]. Concurrently, PGC is usually diagnosed in Caucasians with higher social status, better financial conditions, and a male-to-female ratio of 5:1 [6]. The retrospective study showed that PGC is often diagnosed early in male patients >60 years old without a history of ulcers [13].

Other factors affecting the population distribution that have gradually drawn researchers' attention include personal cancer history, high body mass index, and environmental toxin exposure, which are the independent risk factors for early PGC and advanced PGC [14]. Conversely, family cancer history was the independent risk factor for early DGC [15].

Etiology and cell sources

The ultimate pathogenesis of GC is still unclear. Different pathogenesis might lead to DGC, including two main benign gastric diseases: chronic atrophic gastritis (odds ratio [OR] = 3.92) and intestinal metaplasia (IM), led by gastroesophageal reflux disease (GERD) (OR = 10.08) [16]. Moreover, GC is related to various factors that vary with tumor locations (Figure 2).

Helicobacter pylori infection

This infection has been considered as the class I carcinogen for GC [17]. The correlations between *H. pylori* and tumor locations are still a hot topic under investigation. The process of non-cardia GC might be linked to the inflammatory-response activation induced by *H. pylori*, and the mechanisms involving apoptosis promotion, p53-degradation facilitation, and DNA-mutation accretion are stimulated by metabolite accumulation. The developing process of GC—"The cascade of Correa," followed by chronic superficial gastritis, atrophic gastritis, IM, and atypical hyperplasia—is thus set off. Cytotoxin-associated gene A in *H. pylori* may significantly increase the risk of atrophic gastritis and DGC [6].

Whether *H. pylori* infection causes PGC has perplexed scientists for decades. The decreased gastric-acid secretion induced by gastric mucosa atrophy might have several outcomes after *H. pylori* infection. It facilitates the colonization and reproduction of gastrointestinal microbiota and prevents reflux diseases such as GERD and Barrett's esophagus (BE), thus decreasing the occurrence rate of PGC to some extent [18]. The eradication of *H. pylori* might hasten the onset of PGC through the reflux diseases—chronic atrophic gastritis—GC pathway, which has been identified in the developed countries. However, some studies found an opposite trend in the developing countries that *H. pylori* infection is positively related to PGC, thereby

proving that *H. pylori* cause PGC via mechanisms similar to DGC [19]. However, another study showed that *H. pylori* are only related to carcinogenesis in metastasis from distant gastric to the gastric body and bottom, while *H. pylori* merely caused atrophic gastritis instead of cancer while colonizing pylorus [20]. In conclusion, the correlation between *H. pylori* and PGC is unclear, but those described here may avail the clinicians with an improved treatment plan in the future.

Lifestyle

Lifestyle affects the GC progress in many ways, including smoking, drinking, high-salt food, food with carcinogens, and inadequate physical activity. Smoking is a known risk factor for DGC and may increase PGC risk by 2- to 6-fold [21]. A previous study [22] showed that the combined effect of smoking and drinking promotes the progress of gastric cardia cancer despite a weak linkage between alcohol and PGC. A high-salt diet is an independent risk factor for distal gastric intraepithelial neoplasia [23], damaging the gastric mucosa exposed to the toxic microenvironment and expediting carcinogenesis. Agudo et al. [24] concluded that low-grade chronic inflammation caused by diet habits was positively relevant to PGC by analysing the large samples of patients and the inflammatory score of the diet in Europe. Nitrite and its ramification, N-nitrosodimethylamine, act as indirect carcinogens that cause GC when consumed in high doses [25] and function synergistically with *H. Pylori* in carcinogenesis.

H. pylori also promote nitroso flora growth, inhibit vitamin C secretion, and increase gastric nitrite [26]. Some lifestyles may prevent gastric carcinogenesis. Anti-oxygen contained in fresh vegetables and fruits reduce the risk of both DGC and PGC [27]. Physical exercise reduces the risk of PGC (OR = 0.80; 95% confidence interval [CI], 0.63–1.00) and DGC (OR = 0.63; 95% CI, 0.52–0.76) [28]. Especially in females, long-term and high-dose

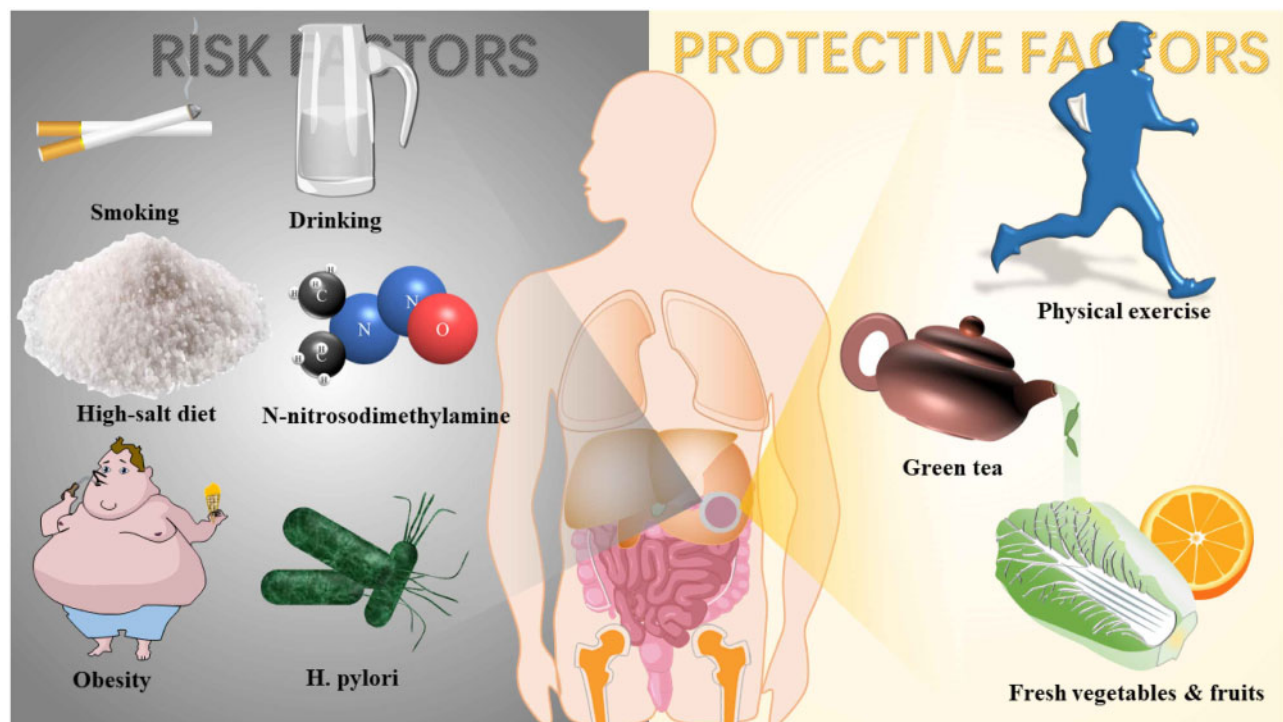


Figure 2. Some risk and protective factors of gastric cancer.

green-tea drinking reduces the risk of DGC (hazard ratio = 0.79; 95% CI, 0.65–0.96) because of the polyphenol and phytoestrogen content in green tea [29].

Precancerous conditions and lesions

Esophageal cancer, PGC, and DGC are three independent cancer subtypes known for precancerous lesions and cell sources. Nevertheless, the overlapping definitions of those precancerous lesions usually create confusion. IM, BE, and GERD have overlapping concepts. IM refers to metaplasia mainly in the stomach and esophagus, where the intestine-resembling epithelium replaces the intrinsic cells. BE refers to the squamous-to-columnar epithelium metaplasia in the esophagus >1 cm, which contains goblet cells and three types of epithelia (specialized columnar, junctional, and atrophic gastric fundic-type epithelium) [30]. BE is a specific IM in the esophagus that is less aggressive than short-segment IM [31]. Although these are parallel to precancerous lesions, GERD is known to be the main reason for IM (especially in the proximal position of the stomach) and BE (especially in the distal location of the esophagus). Even without a direct correlation with PGC or DGC development, discussion of these precancerous conditions and lesions helps to elucidate the progression of carcinogenesis.

The renewal of the concept “gastric cardia” further clarifies the definitions of these concepts. Gastric cardia was considered an intrinsic structure connecting the esophageal squamous epithelium and gastric columnar epithelium, and was redefined by Chandrasoma in 1997 [32]. He pointed out that gastric cardia—the specialized intestinal mucosa lacking goblet cells—is an acquired elongated structure formed by GERD-induced squamous-to-columnar epithelium metaplasia, indicating the severity of GERD. It also acts as a precursor for both proximal gastric IM and distal esophageal BE.

Spasmodic polypeptide-expressing metaplasia (SPEM) is an untypical mode of metaplasia that contains goblet cells and has gained increasing attention. Based on the features of deep antral gland cells and duodenal Brunner gland cells, SPEM expresses biomarkers, including trefoil factor 2 (TFF2), mucin 6 (MUC6), griffonia simplicifolia lectin II (GSII), cluster-of-differentiation gene 44 variant isoform 9 (CD44v9), and protease inhibitor HE4 (WFDC2) [33]. Histologically, it showed typical features like oxyntic atrophy (loss of corpus chief and parietal cells), surface mucous pit-cell hyperplasia, mucous metaplasia (MM), and pseudo-pyloric metaplasia (PM). Characterized by the TFF2+ in the shape of large foam, SPEM-MM expresses the molecule of CD44 and SOX9, secretes neutral or acidic mucins, and substitutes the function of the lost chief and parietal cells. Moreover, SPEM-PM is poorly differentiated pyloric-gland-like cells that occur after SPEM-MM and serve as the precursors of gastric dysplasia, thereby initiating the process of malignant transformation [34].

Differentiated from gastric glandular isthmus stem cells or matured chief cells, SPEM acts as the precursor of IM and helps the cells enter into transdifferentiation [31]. Whether it is relevant with Lgr5+ chief cells, the original cells of GC, remains unclear [34, 35]. As a reparative mechanism at the beginning of injury, SPEM serves as a highly localized metaplasia that may become malignant with chronic inflammation and subsequent injury.

SPEM can also coordinate with *H. pylori*, a carcinogen, to strengthen its carcinogenesis function [36]. Sialyl-Lewis-X (sLe^x) is widely expressed in the gastric gland cells and spreads from the surface to the bottom of the gastric gland during SPEM.

Adhesin SabA is anchored on the surface of *H. pylori* and is a target of sLe^x. When SabA and sLe^x combine, *H. pylori* invades into the bottom of the gastric gland for survival. With the expansion of SPEM, *H. pylori* migrate from the gastric antrum to the corpus and fundus, which enlarges the ecological niche of *H. pylori* and finally causes upper GC.

Typically, GC is derived from the abnormal differentiation of stem/progenitor cells under specific conditions, albeit the primary cells of PGC and DGC are still under discussion. Based on the perspective of embryonic development, the endoderm is differentiated into the stratified squamous epithelium, whose basal cells—the P63⁺ ancestral cells—are primarily distributed in the cardiac sinus. The P63⁺KRT5⁺KRT7⁺ basal progenitor cells and the new transitional columnar epithelium in the esophageal-gastric junction are differentiated into intestine-like cells that reproduce the IM process CDX2 expression [19]; these are the initial cells of PGC [37]. Another study suggested that IM development and tumor progression are two different processes, as CDX2 expression and prognosis are positively correlated. Moreover, Lgr5⁺CCKBR⁺ stem cells are partly expressed in gastric cardia, functioning as the original cells of PGC [19].

Interestingly, there are various views on the origin cells for DGC. Most studies proposed that Lgr5+ stem cells located primarily on the fundus of lower gastric foveola were the original cells, as they triggered DGC via the Wnt-β-catenin pathway following APC loss [38]. A few studies regarded this cluster as the original cells of PGC. MIST1⁺ isthmus stem cells that express Cxcr4 initiate DGC by activating the Cxcl12/Cxcr4 signal axis—an essential precondition of carcinogenesis and a promising target of treatment [39]. Migrating from isthmus to fundus, MIST1⁺ isthmus stem cells reproduce swiftly with KRAS mutation and cover the stomach [34]. Thus, some studies proved that MIST1⁺ isthmus stem cells function as the original cells of DGC and GC in all sites [40]. Other cell clusters with unclear functions may also be related to GC, such as intestinal tufted cells with DCLK1 expression.

With the development of single-cell sequencing combined with spatial transcriptomics, the research of GC has entered a new stage. These new tools offer improved methods to explore the cellular components and differentiation between PGC and DGC, and thus reveal the original cells of PGC and DGC.

Other factors

Genetic factors have accounted for 1%–3% of GC, usually in areas with a low morbidity rate. It contained three primary syndromes: hereditary diffuse GC (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal GC (FIGC). HDGC, featured by CDH1 or CTNNA1 mutation, presents different manifestations in diverse ethnic groups. In Europe and North America, HDGC presents as lesions in the proximal region (from cardiac to pre-pyloric region) but occurs in the distal area in Maori families [41]. GAPPS is a basal gland polypus of the proximal stomach. Irrelevant to its location, FIGC may increase the onset risk of GC in both sites (16 times for non-cardiac GC and 8 times for cardiac GC) when the patients have *H. pylori* infection [16].

Chronic inflammation, whether induced by *H. pylori* or not, also plays a significant role. For example, DNA damage caused by chronic inflammation is the driving force of gastric cardiac cancer via activated mTOR and NF-κB pathways and induces the progression of IM and SPEM [42]. In addition, autoimmune gastritis, in which the autoimmune antibodies attack the

parietal cells, may lead to pernicious anemia and increase the onset risk of DGC without reducing PGC [43].

Furthermore, obesity is the second leading factor causing PGC progression by increasing abdominal pressure to promote gastroesophageal reflux and changing the diet habit to alter the endocrine [44]. Fasting blood glucose also affects gastric carcinogenesis without apparent location influence. Hypoglycemia also increases the onset risk of DGC with almost no effect on PGC [45].

Pathological characteristics

Clinical pathology

Clinicopathological characteristics of GC are linked to their locations. In a survey of 438 patients, the features, including general pathology, histological pathology, lymph-node metastasis, and pathological stage, varied in the early stage between PGC and DGC [46]. Compared with DGC, PGC has the following characteristics: a higher percentage of non-depressed type (including type I, protrude type; type IIa, superficial protrude type; type IIb, superficial flat type), a shorter average diameter, a deeper submucosal invasion, better differentiation condition, and less lymph-node metastasis. Histological pathology revealed that papillary adenocarcinoma and some rare types, such as

mucinous adenocarcinoma, lymphoid stromal cancer, and neuroendocrine carcinoma, are likely to occur in the proximal locations in contrast to the poorly cohesive cancers. PGC has a short survival time, although it is frequently diagnosed in an earlier pathological stage.

Advanced GC shared some common features despite some differences. Some studies [14] revealed PGC characteristics, such as a higher percentage of Borrmann I and II type, lymph-node metastasis, advanced pathological stages, and lower R0 removal rate compared with DGC. Another study supported the above findings with some new features [12]. Compared with PGC, DGC presented a lower organ-removal rate, shorter operation time, less blood loss during surgery, and a higher 5-year survival rate (Table 1).

Lauren classification is a standard classification of GC based on the tumor locations. It divides GC into two types: intestinal and diffuse. The intestinal type has the following characteristics: (i) mainly found in the cardia and gastric fundus; (ii) mostly occurs in the elderly and male patients; (iii) majority of the cells show medium–high differentiation; (iv) has a relatively early staging with improved prognosis. The diffuse type has the following characteristics: (i) frequently occurs in the gastric antrum; (ii) mostly diagnosed in young women; (iii) has higher regional lymph-node metastasis and distant metastasis rates in

Table 1. The characteristics of DGC and PGC

Variable	DGC	PGC	Reference
Regional distribution	Mainly in developing countries	Mainly in developed countries	[4–7]
Population distribution	People with low social status, especially in young black males	Caucasians with higher social status, especially in old male patients	[11–15]
Age (years)	58.9 ± 12.5	64.2 ± 8.1	[46]
Gender (male/female ratio)			[14, 46]
Early GC	2.04:1	2.64:1	
Advanced GC	2.00:1	4.10:1	
Etiology			[17–29]
<i>H. pylori</i> infection	strong correlation	Unclear	
Lifestyle	<ul style="list-style-type: none"> • Risk factors: smoking, high-salt diet, food with carcinogens • Protective factors: fresh vegetables and fruits, physical exercise, green-tea drinking 	<ul style="list-style-type: none"> • Risk factors: smoking (plus drinking), food with carcinogens • Protective factors: fresh vegetables and fruits, physical exercise 	
Clinical pathology			[12, 14, 46]
Early GC	Bigger in size, poor differentiation, more poorly cohesive carcinoma, more lymph-node metastasis, better overall survival	Smaller in size, good differentiation, more tubular and papillary adenocarcinoma, less lymph-node metastasis, worse overall survival	
Advanced GC	Lower organ-removal rate, shorter operation time, less blood loss during surgery	Higher percentage of Borrmann I and II type, lymph-node metastasis, advanced pathological stages, lower R0 removal rate	
Molecular pathology	MSI type	CIN and EBV type; higher expression of TAMs, GR, KLF4, MUC2, G-17	[47, 48]
Manifestations	Regurgitation, eructation, or nausea	Retrosternal pain and progressive dysphagia	[49]
Treatment			[50–76]
Early GC	Endoscopic mucosal resection and endoscopic submucosal dissection		
Advanced GC	Laparoscopic D2 radical gastrectomy with uncut RY anastomosis; FLOT and PF schemes chemotherapy; adjuvant, perioperative, and palliative radiotherapy	Proximal gastrectomy with double-tract reconstruction; neoadjuvant chemoradiotherapy plus adjuvant chemotherapy	
Survival	Higher 5-year survival rate	Lower 5-year survival rate	[46]

GC, gastric cancer; DGC, distal gastric cancer; PGC, proximal gastric cancer; MSI, microsatellite instability; CIN, chromosomal instability; EBV, Epstein-Barr virus; TAMs, tumor-associated macrophages; GR, gastrin receptor; KLF4, Kruppel-like factor 4; MUC2, Mucin 2; G-17, gastrin-17; RY, Roux-en-Y.

the early stage with poor prognosis [77]. In summary, the intestinal type is correlated with PGC, while the diffuse type is associated with DGC. These findings need to be verified further.

Epithelial-mesenchymal transition (EMT) is a hot topic in cancer research. Cancers with EMT embody a high degree of malignancy and poor prognosis. *Helicobacter pylori* infection, the leading risk factor for DGC, may expedite the progression of cancer. The bacteria increase the expression of some molecules, such as soluble heparin-combined epidermal growth factor (HB-EGF), matrix metalloproteinases 7 (MMP-7), and gastrin (polypeptide hormone secreted by the gastric mucosa), followed by E-cadherin cleavage. The PI3K/PKC/NF- κ B pathway activated by gastrin initiates the EMT process and promotes metastasis [78]. Another factor—the tumor parenchymal interstitial ratio—also affects the prognosis of GC. However, the relevance among EMT, tumor parenchymal interstitial ratio, and tumor locations have not yet been clarified. Clinical decision-making and prognosis evaluation may benefit from further exploration in the future.

Molecular pathology

The cancer genome atlas (TCGA) classification

Researchers have put forward a new method of classification—TCGA classification. GC is classified into four types: chromosome instability, microsatellite instability (MSI), genomic stability, and Epstein-Barr virus infection [47]. Accounting for >50% of cancer cases, the chromosome-instability type holds the central position, frequently occurring in the proximal region with RTK–RAS pathway activation and thus causing cancer [14]. MSI primarily occurs in the distal areas, such as the gastric antrum and pylorus, and the majority of the patients are elderly females. DNA hypermethylation is followed by mismatched repair protein MLH1 silencing and inactivation, forming the MSI type, divided into MSI-H and MSI-L subtypes according to the methylation level. Previous studies demonstrated that the MSI-H subtype is presented in the intestinal-type GCs with a better prognosis than the MSI-L and microsatellite-stability subtypes [79]. The lack of cell adhesion caused by a Ras homolog family member A (RHOA) mutation has a mounded stable genomic type and is often diagnosed as diffuse-type cancer with a relatively young population of patients, showing no apparent connection to the tumor location. Epstein-Barr virus-associated GC, caused by methylation-induced CDKN2A silencing, is mainly presented as a lymphoid epithelioma-like carcinoma with a high mutation frequency of PI3K and RA1D1a and the overexpression of PD-L1/2. It occurs in the proximal region of young men and shows an improved prognosis [80, 81] (Figure 3).

Genetic alterations

Common genetic alterations, including genetic overexpression, loss of expression, and expressive suppression, occur in GC as in other cancers. Some of these have shown varied expressions along with the change in tumor locations. Specific genes, such as *Her-2* and *P53*, are often overexpressed in PGC, while *B-cell translocation gene 1* witnesses expressive suppression in PGC.

Researchers have introduced single-nucleotide polymorphisms and epigenetic modifications underlying GC to investigate the mechanisms of gene-expression changes. Single-nucleotide polymorphisms and single-nucleotide mutation at the genomic level are the most common genetic variations. Some nucleotide mutations are significantly capable of changing cancer susceptibility and location preference. The epigenetic mechanisms and heritable changes without nucleotide

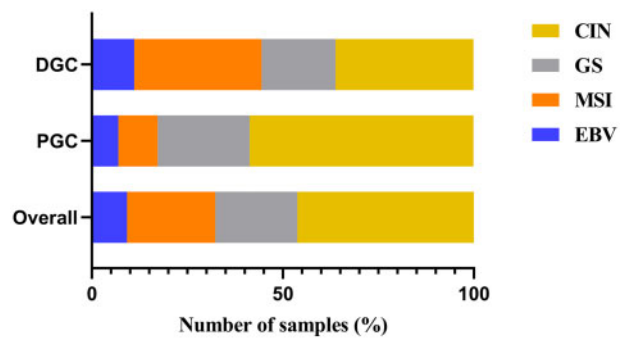


Figure 3. The correlation between TCGA classification and tumor locations in the Chinese population. TCGA, The Cancer Genome Atlas; DGC, distal gastric cancer; PGC, proximal gastric cancer; CIN, chromosomal instability; GS, genomic stability; MSI, microsatellite instability; EBV, Epstein-Barr virus.

mutations also exert some effects. The epigenetic mechanisms involve DNA methylation, histone modification, genomic imprinting, gene silencing, and non-coding RNA dysregulation. DNA methylation is the core of epigenetic mechanisms and plays a dominant role in deciding cancer susceptibility in various locations with different methylation sites. Herein, we listed some genetic alterations that correlate with tumor locations (Table 2).

Moreover, non-coding RNAs—a group of RNA molecules excluded from “features of protein translation”—have recently gained increasing attention. In addition to the functional types such as transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), non-coding RNAs also include long non-coding RNAs (lncRNAs), microRNAs (miRNA), circular RNAs (circ-RNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), extracellular RNA (exRNAs), and small Cajal body-specific RNAs (scaRNAs). These non-coding RNAs may have altered the host-gene expression and promote cancer invasion and metastasis, thereby playing a significant role in carcinogenesis despite their small sizes and qualities. Also, new correlations have been established between some non-coding RNA and tumor locations. Quantitative reverse transcription PCR (RT-qPCR) was applied to detect the expressions of non-coding RNAs in PGC and DGC, which might provide us with more information for the precise treatment for GC in the future (Table 3).

Biomarkers

CEA, CA19-9, CA72-4, and CA125 are the classic biomarkers of GC for diagnosis and prognosis evaluation. Some studies discovered that CEA is highly expressed in DGC with the diagnostic values of other traditional biomarkers [147]. These biomarkers are easily detectable and are promising candidates in identifying tumor locations but necessitating further research.

A lack of specificity and differential diagnostic values have restricted the applications of these traditional biomarkers. Thus, finding novel biomarkers for GC is an urgent requisite. In addition to the gene expression mentioned above, some biomarkers, such as proteins and factors, might indicate the tumor locations and thus function in tumor detection and surveillance. Herein, we listed some typical biomarkers that have a strong diagnostic specificity for GC.

1. *Tumor-associated macrophages (TAMs)*. TAMs are inflammatory cells located in tumor stroma and indicate poor prognosis. TAMs usually occur in gastric cardia, characterized by poor

Table 2. Genetic alterations and their location preferences in gastric cancer

Single-nucleotide polymorphic				DNA methylation			
Polymorphic genes	Location preferences	OR (95% CI)	Ref.	Epigenetic mutations	Methylation site	Location preferences	Ref.
PRKAA1 (rs10074991)	Distal	1.18 (1.12–1.26)	[82]	RASSF1A	Promoter	Proximal	[83]
NFKBIA (rs696 AA)	Proximal	2.23 (1.10–4.55)	[84]	HLTF	CpG island	Proximal	[85]
NFKBIA (rs2233406 CT)	Distal	1.66 (1.01–2.75)		TSP1	Promoter	Proximal	[86]
NFKBIA (rs2233407 CT+TT)	Distal	1.65 (1.01–2.71)		CAV1	CpG island and transcription start site (TSS) regions	Proximal	[87]
NFKB1 (rs3755867 GG)	No statistical difference	1.58 (1.02–2.39)		MEG3	Promoter	Proximal	[88]
P27(kip1) V/V	Proximal	2.01 (1.12–3.68)	[89]	C5orf66-AS1	TSS regions	Proximal	[90]
MTHFR- 677TT	Proximal	2.04 (1.28–3.26)	[91]	Wnt-antagonist genes			[92]
ADPRT (Ala/Ala)	Proximal	2.17 (1.55–3.04)	[93]	sFRP 1	Promoter	Proximal	
XRCC1 (Gln/Gln)	Proximal	1.61 (1.06–2.44)		sFRP 2	Promoter	Proximal	
COX-2 1195AA	Proximal	1.50 (1.05–2.13)	[94]	sFRP 4	Promoter	Proximal	
765GC	Proximal	2.06 (1.29–3.29)		sFRP 5	Promoter	Proximal	
587Arg/Arg	Proximal	1.67 (1.04–2.66)		Wif-1	Promoter	Proximal	
MDM2 -309 GG vs TT	Proximal	2.00 (1.61–2.50)	[95]	Dkk3	Promoter	Proximal	
GT vs TT	Proximal	1.50 (1.20–1.88)		E-cadherin	5' CpG island	Proximal	[96]
PD-1 (rs2227982 C > T) TT vs CC	Proximal	2.53 (1.11–5.79)	[99]	GATA5	Promoter	Proximal	[97]
TT+CT vs CC	Proximal	2.04 (1.01–4.13)		FBXO32	Promoter	Proximal	[98]
MYT1L (rs17039396 AG/GG)	Proximal	0.57(0.40–0.81)	[101]	RKIP	Promoter	Proximal	[100]
XPG (rs751402) C/T	Proximal	1.33 (1.00–1.76)	[102]	Genes	Other genetic alterations	Location preferences	Ref.
T/T	Proximal	1.77 (1.12–3.30)		HER2	Expression in gastric cancer	Proximal	[76]
MMP2 – 1306CC	Proximal	3.36 (2.34–4.97)	[106]	P53	Overexpression	Proximal	[103]
FASL- 844TT or TC	Proximal	4.58 (2.07–10.14)	[107]	BTG1	Expressive suppression	Proximal	[104]
FAS- 1377AA				hTERT	Overexpression	No statistical difference	[105]
				smad4	Loss of expression	Undefined	
				P16	Loss of expression	Undefined	

OR, odds ratio; CI, confidence interval.

differentiation, deep infiltration, and an advanced stage. However, some viewpoints have objected to this relevance [148].

2. *Gastrin receptor (GR)*. GR is a protein expressed mainly in enterochromaffin and parietal cells, and promotes tumor development through several pathways. The expression of GR is significantly higher in PGC [149].

3. *Kruppel-like factor 4 (KLF4) and specificity protein 1 (SP1)*. KLF4 is a transcription factor belonging to the KLF family. It is usually combined with SP1 to inhibit gene expression. The high expression of KLF4 indicates a high onset risk for PGC, while SP1 expression indicates a high onset risk for DGC [150].

4. *Mucin 2 (MUC2) and mucin 6 (MUC6)*. MUC2 and MUC6 are specific mucins expressed in the gastrointestinal tract with differential diagnostic values for PGC and DGC. These mucins are secreted in different parts of the stomach. The higher expression of mucin indicates the diseased location (distal or proximal) of the stomach. Goblet cells in the IM structure secrete MUC2, which is highly expressed in PGC, while MUC6, secreted by gland cells of the gastric corpus and antrum, is highly expressed in DGC [151].

5. *Pepsinogen I/Pepsinogen II ratio (PGR) and Gastrin-17 (G-17)*. PGR and G17 are indicators for tumor locations. Stored in the

gastric wall, pepsinogen is converted into pepsin by gastric acid. Several studies have found that the PGR level drops sharply in PGC, while the G-17 level is elevated in PGC compared with DGC [48].

In addition to the above biomarkers, the others, such as TFF3, E-cadherin, Catenin, CD44v6, tyrosine kinases, platelet-derived growth factor receptor (PDGFR), S100A6, and Cyclin D1/E2, are promising but require additional investigation. Detecting the differential expressions in the proximal and distal gastric sites of humans or mice models with enzyme-linked immunosorbent assay or immunohistochemical methods might identify valuable biomarkers for GC in the future.

Manifestations

Typically, there are some common symptoms in GC patients, such as dyspepsia, anorexia, emesis, gastralgia, and cachexia. However, the clinical manifestations vary with tumor location. PGC patients present retrosternal pain and progressive dysphagia, occasionally resembling esophageal-cancer patients, while DGC often experiences regurgitation, eructation, or nausea due to tumor obstruction in the pylorus. These non-specific symptoms may help in identifying tumor location.

Table 3. Non-coding RNAs and their location preferences in gastric cancer

Long non-coding RNAs	Expression changes	Location preferences	Ref.	Micro RNAs	Expression changes	Location preferences	Ref.	Circular RNAs	Expression changes	Location preferences	Ref.
C5orf66-AS1	Downregulated	Proximal	[90]	miR-770	Downregulated	Proximal	[88]	hsa_circ_002059 (circ_KIAA0907)	Downregulated	Undefined	[108]
LOC100130476	Downregulated	Proximal	[109]	miR-141	Downregulated	Proximal	[110]	hsa_circ_0000745 (circ_SPECC1)	Downregulated	Undefined	[111]
ASHG19A3A028863	Upregulated	Proximal	[112]	miR-203a	Downregulated	Proximal	[113]	hsa_circ_0000181 (circ_TATDN3)	Downregulated	Undefined	[114]
ASHG19A3A040903	Upregulated	Proximal		miR-107 (rs2296616 TC/CC)	Upregulated	Proximal	[115]	hsa_circ_0074362 (circ_ARHGAP26)	Downregulated	Undefined	[116]
ASHG19A3A041865	Upregulated	Proximal		miR-3656	Downregulated	Proximal	[117]	hsa_circ_0003159 (circ_CACNA2D1)	Downregulated	Undefined	[118]
ASHG19A3A018727	Upregulated	Proximal		miR-378c	Downregulated	Proximal		hsa_circ_0000190 (circ_CNIH4)	Downregulated	Undefined	[119]
ASHG19A3A052295	Upregulated	Proximal		miR-628-3p	Downregulated	Proximal		circ_KIAA1244	Downregulated	Undefined	[120]
GUST-20-P1426265844	Upregulated	Proximal		miR-US33-3p	Downregulated	Proximal		hsa_circ_0047905 (circ_SERPINB5)	Downregulated	Undefined	
ASHG19A3A041043	Upregulated	Proximal		miR-148a-3p	Downregulated	Proximal		hsa_circ_0138960 (circ_GDA)	Downregulated	Undefined	
ASHG19A3A033911	Upregulated	Proximal		miR-H10	Downregulated	Proximal		hsa_circ_769015	Downregulated	Undefined	
ASHG19A3A026346	Upregulated	Proximal		miR-638	Downregulated	Proximal		hsa_circ_0013048 (hsa_circ_100269)	Downregulated	Undefined	[121]
ASHG19A3A007184	Downregulated	Proximal		miR-483-5p	Downregulated	Proximal		hsa_circ_001569	Upregulated	Undefined	[122]
ASHG19A3A018598	Downregulated	Proximal		miR-675-5p	Downregulated	Proximal		hsa_circ_0017639 (circ-SFMBT2)	Upregulated	Undefined	[123]
ASHG19A3A038967	Downregulated	Proximal		miR-1184	Downregulated	Proximal		hsa_circ_0001821 (circPVT1)	Upregulated	Undefined	[124]
ASHG19A3H0000023	Downregulated	Proximal		miR-299-5p	Downregulated	Proximal		hsa_circ_0000284 (circHIPK3)	Upregulated	Undefined	[125]
ASHG19A3A018662	Downregulated	Proximal		miR-4285	Downregulated	Proximal		hsa_circ_0001946 (cirs-7)	Upregulated	Undefined	
ASHG19A3A007413	Downregulated	Proximal		miR-3665	Downregulated	Proximal		hsa_circ_0064644 (circRMS3)	Upregulated	Undefined	
ASHG19A3A011053	Downregulated	Proximal		miR-H25	Downregulated	Proximal		hsa_circ_0056618	Upregulated	Undefined	
ASHG19A3A035937	Downregulated	Proximal		miR-H17	Downregulated	Proximal		hsa_circ_0027599	Downregulated	Undefined	
ASHG19A3A055173	Downregulated	Proximal		miR-3195	Downregulated	Proximal		hsa_circ_0007766 (circ_ERBB2)	Upregulated	Undefined	
ASHG19A3A0001119	Downregulated	Proximal		miR-518e-5p	Downregulated	Proximal		hsa_circ_0000267	Upregulated	Undefined	
HOTAIR	Upregulated	Undefined	[126]	miR-3196	Downregulated	Proximal		hsa_circ_0089548 (circ-NOTCH1)	Upregulated	Undefined	
H19	Upregulated	Undefined	[127]	miR-30d-5p	Downregulated	Proximal		hsa_circ_0089547 (circ-NOTCH1)	Upregulated	Undefined	
CCAT1	Upregulated	Proximal	[128]	miR-3124-5p	Downregulated	Proximal		hsa_circ_0067997	Upregulated	Undefined	

(continued)

Table 3. (continued)

Long non-coding RNAs	Expression changes	Location preferences	Ref.	Micro RNAs	Expression changes	Location preferences	Ref.	Circular RNAs	Expression changes	Location preferences	Ref.
AP001631.9	Upregulated	Undefined	[129]	miR-196a-5p	Upregulated	Proximal		hsa_circ_0004771 (circ_NRIP1)	Upregulated	Undefined	
ATB	Upregulated	Undefined	[130]	miR-135b-5p	Upregulated	Proximal		hsa_circ_0017728	Upregulated	Undefined	
GACAT1	Upregulated	No statistical difference	[131]	miR-2355-3p	Upregulated	Proximal		hsa_circ_0081143	Upregulated	Undefined	
FENRR	Downregulated	Undefined	[132]	miR-4307	Upregulated	Proximal		hsa_circ_0042881 (circNF1)	Upregulated	Undefined	
FER1L4	Downregulated	Undefined	[133]	miR-1244	Upregulated	Proximal		hsa_circ_0032627 (circDLST)	Upregulated	Undefined	
MALAT1	Upregulated	Undefined	[134]	miR-892a	Upregulated	Proximal		hsa_circ_0093398 (circPDS1)	Upregulated	Undefined	
HULC	Upregulated	No statistical difference	[135]	miR-20a-5p	Upregulated	Proximal		hsa_circ_0010522 (circS-133)	Upregulated	Undefined	
ZNFX1-AS1	Upregulated	No statistical difference		miRPlusA1087	Upregulated	Proximal		hsa_circ_0092303 (circCACTIN)	Upregulated	Undefined	
HOXA	Downregulated	Undefined	[136]	miR-93-5p	Upregulated	Proximal		hsa_circ_0008035	Upregulated	Undefined	
HOTTIP	Upregulated	Undefined	[137]	miR-455-3p	Upregulated	Proximal		hsa_circ_0008365 (circ-SERPINE2)	Upregulated	Undefined	
HOXA13	Upregulated	Undefined		miR-105-5p	Upregulated	Proximal		hsa_circ_0090410 (circUBA1)	Upregulated	Undefined	
MSTO2P	Upregulated	No statistical difference	[138]	miR-764	Upregulated	Proximal		hsa_circ_0005075 (circ-EIF4G3)	Upregulated	Undefined	
AFAP1-AS1	Upregulated	Undefined	[139]	miR-130b-5p	Upregulated	Proximal		hsa_circ_0008549 (circOSBPL10)	Upregulated	Undefined	
ANRIL	Upregulated	Undefined		miR-506-3p	Upregulated	Proximal		hsa_circ_0000199 (circAKT3)	Upregulated	Undefined	
CASC15	Upregulated	Undefined		miR-454-3p	Upregulated	Proximal		hsa_circHECTD1	Upregulated	Undefined	
GAPLINC	Upregulated	Undefined		miR-142-3p	Upregulated	Proximal		hsa_circ_0009109 (circ-DCAF6)	Upregulated	Undefined	
LINC00673	Upregulated	Undefined		miR-3591-3p	Upregulated	Proximal		hsa_circ_0031250 (circ-PRMT5)	Upregulated	Undefined	
PANDAR	Upregulated	Undefined		miR-196b-5p	Upregulated	Proximal		hsa_circ_0003855 (circDUSP16)	Upregulated	Undefined	
PVT1	Upregulated	Undefined		miR-3664-5p	Upregulated	Proximal		hsa_circ_0069086 (circMAN2B2)	Upregulated	Undefined	
Sox2ot	Upregulated	Undefined		miR-636	Upregulated	Proximal		hsa_circ_0058147 (circFN1)	Upregulated	Undefined	
UCA1	Upregulated	Undefined		miR-1	Upregulated	Undefined	[140-142]	hsa_circ_0000467	Upregulated	Undefined	
XIST	Upregulated	Undefined		miR-34	Upregulated	Undefined		hsa_circ_0003221 (circPTK2)	Upregulated	Undefined	
ZEB1-AS1	Upregulated	Undefined		miR-423-5p	Upregulated	Undefined		hsa_circ_0063526 (circ-RanGAP1)	Upregulated	Undefined	
ZFAS1	Upregulated	Undefined		miR-20a	Upregulated	Undefined		hsa_circ_0066436 (circATXN7)	Upregulated	Undefined	

(continued)

Table 3. (continued)

Long non-coding RNAs	Expression changes	Location preferences	Ref.	Micro RNAs	Expression changes	Location preferences	Ref.	Circular RNAs	Expression changes	Location preferences	Ref.
				miR-17-5p	Upregulated	Undefined		hsa_circ_0040809 (circBANP)	Upregulated	Undefined	
				miR-21	Upregulated	Undefined		hsa_circ_0077736 (circ-CEP85L)	Downregulated	Undefined	
				miR-106a	Upregulated	Undefined		hsa_circ_00074444 (circRHOBTB3)	Downregulated	Undefined	
				miR-106b	Upregulated	Undefined		hsa_circ_101057 (circLARP4)	Downregulated	Undefined	
				miR-1233	Downregulated	Undefined		hsa_circ_0000096	Downregulated	Undefined	[144]
				miR-593-5p	Downregulated	Undefined	[143]	circMLLT10	Upregulated	Undefined	[145]
								circNHSL1	Upregulated	Undefined	[146]
								circCCDC9	Downregulated	No statistical difference	

Treatment and prognosis

Surgical treatment

Early GC

Endoscopic mucosal resection and endoscopic submucosal dissection (ESD) are adopted to treat early GC. Clinicians use endoscopic mucosal resection to treat cancers with small diameters and superficial infiltration [50]. Since ESD has been adopted frequently in cancers invading submucosa layers, it gradually became the first-line treatment for early GC [51]. Patients who underwent ESD could achieve a 94.9% overall resection rate and 97.1% 5-year survival rate, suggesting that it is a safe and effective treatment for early GC [52]. Although it has satisfactory outcomes in both PGC and DGC, the effectiveness is better in treating early PGC.

Advanced GC

Operation-based multidisciplinary treatment has become the therapeutic principle of advanced GC with D2 radical gastrectomy as the primary surgical method. However, how to perform resection and reconstruct the digestive tract is a significant issue for clinicians.

Based on Siewert classification, Western clinicians classified PGC into three types with diverse therapeutic choices. Transthoracic subtotal esophageal resection plus proximal gastrectomy with gastric pull-up reconstruction is adopted to treat type I tumors. Transhiatal extended gastrectomy plus distal esophageal resection with Roux-en-Y (RY) esophagojejunostomy reconstruction is suitable for type III tumors [53]. Transhiatal proximal gastrectomy with double-tract reconstruction might be the best choice for specific type II tumors, with a non-poorly cohesive, intestinal type of Lauren grading 1 or 2 without clinical signs of lymph-node metastasis at the distal stomach [54]. Experts recommended that patients with >3 cm esophageal invasion require transthoracic proximal gastrectomy, which shows fewer risks and better outcomes.

Chinese clinicians prefer proximal gastrectomy (PG) in PGC patients, especially in Ia and Ib stages, since it has a high remission rate and security. Several studies [55] regarded PG as the best surgical choice for PGC, with a better prognosis and shorter resection margins than total gastrectomy [56], despite the complications, such as anastomotic stenosis and reflux esophagitis. Traditional surgical methods, such as esophagogastrectomy, jejunal interposition, jejunal pouch interposition, and double-tract and gastric tubular reconstruction, play significant roles in post-operative digestive-tract reconstruction, albeit with some limitations [57]. For example, the double tract, which has better feasibility and security than others, is now considered the best method for reconstruction [58]. Although new methods, such as the double-flap technique [59], tri-double-flap hybrid method [60], and Cheng's giraffe reconstruction [61], may have some potential functions, researchers regard proximal gastrectomy with double-tract reconstruction as the best surgical choice for PGC.

Laparoscopic D2 radical gastrectomy showed a similar 3-year disease-free survival rate to the typical open resection, rendering it the best surgical choice for most DGCs [62]. Clinicians recommended laparoscopic surgeries to patients in stages I, II, and IIIa with tumor invasion less than the T4a stage or those needing short-circuit operations in late stages. Open operations are worthy for late-stage patients (situated in stage IV or more than T4a stage). The traditional reconstruction of DGC—Billroth I anastomosis, Billroth II anastomosis, and RY anastomosis is controversial [63]. Due to physiological advantages, Billroth I

anastomosis is widely used despite the high risk of anastomotic leakage. If the issue of anastomotic leakage is resolved, Billroth II anastomosis might increase post-operative alkaline reflux gastritis, esophagitis, and anastomotic ulcer. RY anastomosis, another widely used method, usually causes reverse intestinal peristalsis and RY retention syndrome. Uncut RY (U-RY) is a newly proposed reconstruction method that has attracted people's attention. Gastrojejunostomy, jejunojunostomy, and input loop blockage based on preserved intestinal continuity improves the shortages of RY. Compared with traditional RY anastomosis, U-RY shortens the operation time, reduces the post-operative complications, delays gastric emptying, and enhances serum albumin levels, thereby proving to be the best choice of reconstruction nowadays [64].

Chemotherapy

Chemotherapies, classified as neoadjuvant chemotherapy, perioperative chemotherapy, and adjuvant chemotherapy by treatment opportunities, are suitable for advanced GC. Patients with advanced PGC are sensitive to more frequently recommended chemotherapy. Clinical research has demonstrated that neoadjuvant chemotherapy increases the R0 resection rate, pathological complete response rate, and 5-year survival rate of PGC patients [65]. Therefore, national guidelines have listed four cycles of preoperative FLOT (docetaxel, oxaliplatin, 5-fluorouracil, and leucovorin) as the first-level neoadjuvant chemotherapy scheme, followed by the second level of neoadjuvant chemotherapy schemes, such as PF (5-fluorouracil and cisplatin), XELOX (oxaliplatin and capecitabine), capecitabine, and FLOFOX (oxaliplatin and 5-fluorouracil). The perioperative FLOT scheme showed more advantages than adjuvant chemotherapy and was recommended as the primary chemotherapy for PGC patients with locoregional advanced potentially resectable tumors in Western countries [66], especially in cT2 or higher stages, according to National Comprehensive Cancer Network (NCCN) guidelines [67].

Advanced DGC, with less sensitivity to chemotherapy, has benefited less from traditional chemotherapy. Thus, national guidelines chose the FLOT and PF schemes as the second-level recommendations, while the XELOX and the FLOFOX schemes are the third-level recommendations [68]. However, some researchers [69] have suggested that taxanes significantly improve the progression-free survival and overall survival of DGC and intestinal GC compared with PGC and diffuse-type. Furthermore, another study demonstrated that the PFtax scheme—a typical PF scheme combined with docetaxel—presented better progression-free survival and overall survival in DGC patients, promising clinical application [70].

Except for the schemes above, the DCF scheme (docetaxel + cisplatin + 5-fluorouracil) presented palliative chemotherapeutic value for late-stage GCs without an operational chance [71].

Radiotherapy

The application of radiotherapy in GC has attracted researchers' attention since the publication of the INT-0116 research. Patients who have undergone D1 gastrectomy with high-grade GC need adjuvant radiotherapy [72]. Palliative radiotherapy for stage IV is also beneficial [73].

PGC shows better radiotherapeutic value than tumors located in other sites. Therefore, clinicians usually conduct radiotherapy together with chemotherapy, which has more advantages than

neoadjuvant chemotherapy. National guidelines regarded preoperative chemoradiotherapy as the third-level recommendation for advanced PGC. Neoadjuvant chemoradiotherapy plus adjuvant chemotherapy is the best choice for PGC patients nowadays [68].

Although neoadjuvant radiotherapy shows no apparent advantages for advanced-DGC patients [74], adjuvant, perioperative, and palliative radiotherapy has some clinical benefits for DGC.

Targeted therapy and immunotherapy

With the discovery of drug targets and the development of targeted drugs, targeted therapy has become a promising treatment for GC. Multiple targeted therapy schemes have been conducted for patients with single/multi-target susceptibility, such as targeted drugs for EGFR, HER2, FGFR, MET, VEGFR2, PD-1, and CLDN18.2. The detection of HER2, PD-L1, MSI, Epstein-Barr virus (EBV), and Tumor Mutation Burden (TMB) is a regular program for those who undergo gastrectomy [68].

The therapeutic strategies vary with tumor locations. For example, Apatinib mesylate (highly selective VEGFR2 inhibitor), nivolumab, and pembrolizumab (immune checkpoint inhibitors) are suitable for late-stage PGC [75]. In addition, since HER2 overexpression significantly occurs in PGC than DGC, anti-HER2 therapy may be beneficial for PGC patients [76]. In conclusion, therapeutic methods targeting different locations of GC deserve additional research.

Nonetheless, additional clinical trials are needed to explore the therapeutic methods and treatment combinations for PGC and DGC. With research development, patients with PGC or DGC might receive better treatment for prolonged survival time and enhanced treatment outcomes.

Prevention

Considering the risk and protective factors discussed above, researchers have recommended the following methods to prevent GC occurrence (Figure 2).

1. *Lifestyle transformation.* Developing good habits is the most crucial and practical way to prevent GC. On the other hand, bad habits, such as drinking, smoking, and a high-salt diet, are associated with GC development. In contrast, good habits, such as exercising, a regular diet of vegetables and fruits, and drinking green tea, may be beneficial factors [72]. Thus, transforming lifestyles may significantly reduce the onset risk of GCs, irrespective of their locations. Weight control is another valuable method of reducing GERD risks that prevents increased intra-abdominal pressure, improves endocrine disorder, and decreases the onset risk of PGC [152].

2. *Helicobacter pylori eradication.* *Helicobacter pylori* eradication is a widely used prevention measure that successfully reduces the incidence of GC and GC-related deaths, especially for DGC. Whether *H. pylori* eradication is useful in the treatment of PGC is still controversial. Some studies have stated that the bacteria increase the onset risk of PGC because of increasing the GERD possibility. The proton-pump inhibitor (PPI) is a drug conventionally used in eradicating *H. pylori*. It functions by inhibiting gastric-acid secretion, reducing *H. pylori* colonization, and controlling related symptoms. However, long-term usage of PPI may lead to hypergastrinemia, thus promoting PGC development [19]. Therefore, proper use of PPI is essential to prevent PGC.

3. *Antioxidants*. Vitamin C, vitamin E, β -carotene, and lycopene are the most common antioxidants with antitumor functions. These may reduce the onset risk of PGC, as oxidative stress serves as the risk factor for various gastrointestinal diseases [153], while some adverse opinions have proposed that antioxidants increase the total mortality of GC without a preventive effect [154]. Therefore, its function in GC is still controversial.

4. *COX-2 inhibitor*. Smoking, acidic condition, and *H. pylori* infection increase the expression of COX-2, which might cause the atrophy-IM process and finally lead to GC, especially DGC. The COX-2 inhibitor is deemed to reduce the onset risk of DGC; whether it exerts a protective effect in PGC has not yet been verified [155].

5. *Ornithine decarboxylase (ODC) inhibitor*. BE is the precursor lesion of PGC that is correlated with the ODC activity. The ODC inhibitor exerts a protective effect on PGC. α -Difluoromethyl ornithine and troglitazone are the most common ODC inhibitors that reduce the risk of onset of the disease [6, 156]. However, additional clinical trials are required to demonstrate its safety and effectiveness in clinical use.

6. *Endoscopic surveillance*. Regular endoscopic surveillance is a frequently used method to diagnose GC in the early stage. Clinicians have recommended regular endoscopic surveillance for the population who are susceptible to GC, especially those suffering from *H. pylori* infection and precancerous lesions or having familial histories of GC [157].

Conclusion

In summary, we found many differences between PGC and DGC in epidemiological characteristics, etiology, cell source, pathology characteristics, gene expression, molecular markers, manifestations, treatment, prognosis, and prevention. With the development of precision medicine, it is an urgent task to explore the differences among tumor locations. Traditional comparison analysis has helped researchers to discover the apparent diversity of GC, while new techniques, such as artificial-intelligence imaging and single-cell RNA sequencing, might improve the understanding of the process of carcinogenesis and regional differences. These differences would guide diagnosis and treatment, and serve as a promising approach in improving the long-term survival rates and quality of life for patients.

Authors' Contributions

Y.Z., P.S.Z., and C.H. conceived of and designed the project. Y.Z., P.S.Z., Z.Y.R., and C.H. wrote, reviewed, and revised the manuscript. C.H. supervised the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

None declared.

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