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Clinicopathological Characteristics and Pathogenesis of Gastric Cancer at Different Tumor Sites

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Abstract

Gastric cancer is one of the most common malignant tumors in the world. The incidence and mortality of gastric cancer rank high not only in China, but also in the world. In recent years, with the deepening of research on gastric cancer, it has been gradually found that gastric cancer in different locations (gastric antrum, gastric body, gastric fundus and cardia, etc.) is different in pathogenesis, clinicopathological characteristics, molecular biological characteristics, and prognosis of patients. This article reviews the differences in epidemiology, pathological and clinical characteristics, pathogenesis and the research progress of diagnosis and treatment of gastric cancer at different sites, so as to provide ideas and theoretical basis for the precise treatment of gastric cancer in China.

Keywords

Gastric Cancer, Different Tumor Sites, Research Progress

1. Introduction

Gastric cancer is one of the most common malignant tumors of the digestive system, and its incidence and mortality rank the fifth and fourth [1] respectively among all malignant tumors in the world. The incidence and mortality of gastric cancer in China are higher than those in other countries, and the incidence and mortality of gastric cancer are ranked the third [2] among all malignant tumors. Despite the progress of diagnosis and treatment technology in recent years, the 5-year survival rate of gastric cancer is still less than 30%, especially for patients with advanced gastric cancer [3]. The clinicopathological characteristics and bi-

ological behavior of gastric cancer are highly heterogeneous, and this heterogeneity is closely related to the location of the tumor. Many studies have shown [4] [5] that there are significant differences in the epidemiological distribution, pathological types, molecular mechanisms and treatment response of gastric cancer at different sites, such as the antrum, body, fundus and cardia. This phenomenon has become an important focus of basic research and clinical practice of gastric cancer. Although many breakthroughs have been made, the current research still faces important challenges. For example, the driver gene networks of gastric cancer at different sites have not been fully elucidated, and individualized treatment strategies based on molecular subtyping are still in the exploratory stage. The integration of traditional pathological classification and molecular features has not yet been popularized in clinical practice. This article systematically reviews the epidemiology, clinicopathological characteristics, molecular mechanisms, diagnosis and treatment progress of gastric cancer at different sites, aiming to provide theoretical support for optimizing the precision diagnosis and treatment system of gastric cancer and to look forward to future research directions.

2. Epidemiological and Clinicopathological Characteristics of Gastric Cancer at Different Sites

2.1. Location and Epidemiology of Gastric Cancer

The susceptible areas of gastric cancer were antrum, cardia and body. An analysis of the clinical characteristics of gastric cancer patients who underwent surgical treatment in the general surgery department of a hospital showed [6] that among 1087 patients with advanced gastric cancer, the most common site was the gastric antrum (608 cases, 55.9%), followed by the gastric fundus and cardia (249 cases, 22.9%) and the gastric body (173 cases, 15.9%). The antrum of stomach is a high incidence area of gastric cancer, and its incidence is significantly correlated with *H. pylori* infection.

Helicobacter pylori tends to colonize the gastric antrum. The toxins such as CagA and VacA secreted by *H. pylori* can induce chronic inflammation and gastric mucosal atrophy, which gradually evolve into intestinal metaplasia, dysplasia, and eventually lead to cancer [7]. Studies have shown [8] that the high incidence of gastric antral cancer in East Asia is closely related to the high infection rate of *Helicobacter pylori* (most East Asian strains carry the highly virulent CagA gene) and dietary habits (high salt and pickled food). The incidence of gastric fundus and cardia cancer is on the rise in Europe and America, which may be related to obesity, gastroesophageal reflux disease (GERD) and high-fat diet and other factors. Its mechanism is different from that of gastric antrum cancer, which is less dependent on *Helicobacter pylori* infection and more related [9] to Barrett's esophagus, smoking and other factors. Therefore, the proportion of gastric cardia cancer is low in East Asia, while the proportion of gastric cardia cancer is significantly increased in Western countries due to the high

incidence of dietary structure and metabolic diseases. Gastric body cancer is often associated with autoimmune gastritis (e.g., pernicious anemia) or diffuse type of gastric cancer (e.g., signet ring cell carcinoma), which usually presents with extensive invasion and a poor prognosis. Some cases are associated with hereditary diffuse gastric cancer syndrome (HDGC), driven [10] by mutations in the CDH1 gene. The location and geographical distribution of gastric cancer are affected by the interaction of many factors. The high incidence of gastric antrum cancer in East Asia is closely related to *Helicobacter pylori* infection and dietary patterns, while the rising trend of gastric cardia cancer in Europe and the United States suggests that attention should be paid to metabolic diseases and lifestyle changes. Future research needs to combine molecular epidemiology and personalized screening to further optimize prevention and treatment strategies.

2.2. Pathological and Clinical Features

Gastric cancer at different sites shows different pathological and clinical characteristics. Gastric antrum cancer is an intestinal type of gastric cancer driven by *Helicobacter pylori*. Studies have shown [11] that the Lauren classification of gastric antrum cancer is mainly intestinal type, while the Borrmann classification is mainly ulcerative type (type II and type III). This type of tumor has a relatively clear boundary, and is often accompanied by mucosal atrophy and intestinal metaplasia. The main histological type is well-moderately differentiated tubular adenocarcinoma, which accounts for about 70% of all gastric antral cancers. The cancer cells are arranged into tubular structures and are highly differentiated. A few are mucinous adenocarcinoma, which has a poor [12] prognosis. According to clinical guidelines [13], the early symptoms of gastric antral carcinoma are dull pain and fullness in the upper abdomen, which is easily confused with chronic gastritis. In advanced stage, pyloric obstruction may occur, which is caused by tumor invasion of the pylorus leading to gastric emptying disorder, causing vomiting and metabolic disorders. In addition, vascular invasion can lead to melena or hematemesis. The main mode of metastasis is perigastric lymph node metastasis, and hematogenous metastasis is rare. Studies have shown [14] that cancer of the gastric fundus and cardia is a diffuse type of gastric cancer related to metabolic diseases. Its pathological characteristics are mainly diffuse type of gastric cancer and strong invasion. The typical manifestation of Borrmann type is type IV, the so-called "leather stomach", in which tumor cells diffusely infiltrate the whole layer of the gastric wall, resulting in stiffness of the gastric wall and loss of peristalsis. The main histological types of gastric fundus and cardia carcinoma were signet ring cell carcinoma and poorly differentiated adenocarcinoma. The cells were infiltrated in single or cluster, and the mucus secretion was vigorous. The early warning symptoms are retrosternal burning and swallowing foreign body sensation, which are often misdiagnosed as gastroesophageal reflux disease (GERD). In the advanced stage, it manifests as progressive dysphagia due to tumor invasion

of the lower esophagus or cardiac sphincter. In addition, peritoneal implantation metastasis, that is, carcinogenic ascites caused by peritoneal dissemination, can occur, and the prognosis is extremely poor. Its metastasis pattern is mainly mediastinal, celiac trunk lymph node metastasis and peritoneal metastasis [13]. Gastric body cancer is a heterogeneous gastric cancer with a tendency of hematogenous metastasis. Its pathological characteristics are both intestinal type and diffuse type, and its pathological heterogeneity is significant [15]. Compared with gastric antrum cancer, gastric body cancer has a higher proportion of diffuse adenocarcinoma, which is more common in young patients and has a poor prognosis. Vitamin B12 malabsorption due to intrinsic factor deficiency is common. In hematogenous metastasis, liver metastasis caused by portal vein system accounts for about 40%, followed by lung and bone metastasis. In lymph node metastasis, the involvement rate of left gastric artery and splenic hilum lymph nodes is higher [13].

3. The Pathogenesis of Gastric Cancer at Different Sites

3.1. Pathogenesis of Gastric Antral Carcinoma

3.1.1. *H. pylori*-Driven Chronic Inflammation and Genomic Instability

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerobic, spiral-shaped bacterium. Its natural host is the human stomach, with a preference for the antrum region [16] [17]. Its virulence factor, Cag pathogenic island (cag PAI), is a 40-kb gene cluster containing 27 - 31 genes that encode the CagA protein and components [18] [19] of the type IV secretion system (CAG-T4SS). Cag-T4SS infuses CagA into gastric epithelial cells [20], which are phosphor [21] ylated by the host Src/Abl tyrosine kinase via the EPIYA motif. Phosphorylated CagA binds to signaling molecules such as SHP2, Csk, Grb2 and Crk through the SH2 domain, and activates SHP2 to trigger the Ras-Erk pathway and promote mitosis [22]. Nuclear ERK further phosphorylates ELK1, which binds to SRF at the SRE site and induces immediate early gene expression [23] such as c-Fos/c-Jun. The AP-1 transcription factor of c-Fos/c-Jun activates Cyclin D expression, which promotes Cyclin D-CDK4/6 to phosphorylate pRB and release E2F, driving cells into S phase [24]. Cyclin E-CDK2 complex then phosphorylates MCM helicase to initiate DNA replication, leading to abnormal proliferation, while unphosphorylated CagA acts [25] by disrupting the E-cadherin/β-catenin complex. Cadherins mediate cell-cell adhesion, and β-catenin binds to α-catenin to link E-cadherin and the actin skeleton [26]. The release of β-catenin complex leads to the accumulation of β-catenin in the cytoplasm and nucleus, forming a complex with Tcf to activate Cyclin D1 and c-Myc genes and promote cell proliferation. Non-phosphorylated CagA activates the Ras-MEK-ERK pathway by binding to Grb2/SOS to further promote cell proliferation [27]. The two CagA modes of action together lead to the transformation of gastric epithelial cells, which has become a key mechanism of gastric carcinogenesis as shown in **Figure 1**.

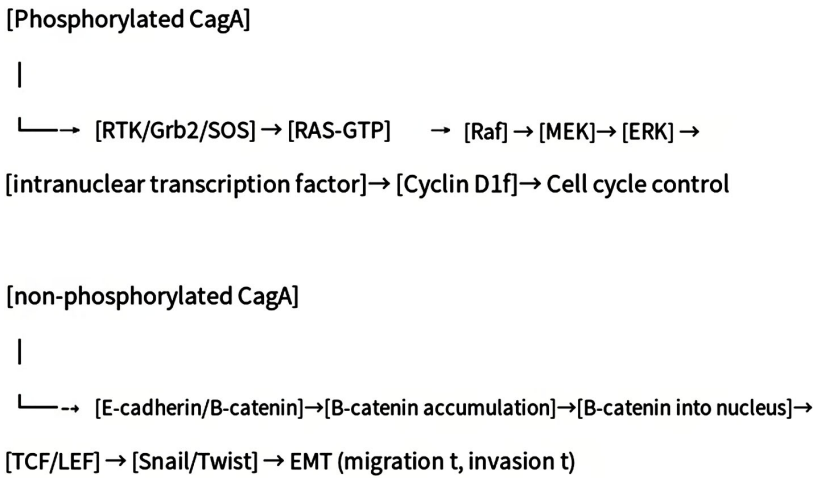

Figure 1. Comparison chart of signal pathways between phosphorylated CagA and non-phosphorylated CagA.

3.1.2. Key Driver Genes and Signaling Pathways

In gastric antral carcinoma, the mutation rate of TP53 gene is as high as 50%. Mutant p53 protein promotes angiogenesis by inhibiting BAX expression and up-regulating VEGF expression. Song, Y *et al.* [28] reported that mutant P53 plays a pro-angiogenic role in gastric cancer tissue by regulating VEGF, thus playing an important role in the occurrence and metastasis of tumors. In addition, HER2 (human epidermal growth factor receptor 2) amplification is present in approximately 15% - 20% of gastric antral carcinomas. The HER2 gene encodes a transmembrane tyrosine kinase receptor that can form a heterodimer with its homologue receptor and continuously activate downstream signaling pathways. Studies have shown [29] that overexpression of HER2 protein significantly promotes the malignant phenotype of tumor cells through the PI3K/AKT/MTOR signaling pathway, including enhanced proliferative activity, inhibition of apoptotic programs, promotion of angiogenesis, and increased metastatic tendency. Specifically, aberrant activation of this pathway can up-regulate cell cycle regulatory proteins (such as Cyclin D1), inhibit pro-apoptotic factors (such as BAD), and regulate ribosome biosynthesis through mTOR, thereby forming a multi-level pro-cancer effect. Based on this molecular mechanism, anti-HER2-targeting drugs such as trastuzumab show therapeutic potential by specifically binding to the extracellular domain of the HER2 receptor and blocking receptor dimerization and downstream signaling. This agent has been shown in clinical trials to prolong the median survival of patients with HER2-positive gastric cancer [30].

3.2. Pathogenesis of Gastric Fundus and Cardia Cancer

3.2.1. EB Virus (EBV) Infection

Epstein-barr virus (EBV) is a human oncogenic virus that is associated with various types of hematological and epithelial malignancies [31] such as nasopharyngeal and gastric cancer. EBV-associated gastric cancer (EBVaGC) accounts for nearly 10% of gastric cancers and is one of the four molecular subtypes proposed

by the Cancer Genome Atlas (TCGA) research network. In terms of molecular alterations, global CpG island hypermethylation is a hallmark of EBVaGC. And it has been found [32] in almost all cases. Notably, in vitro analysis showed that EBV infection induced global CpG island hypermethylation [33]. Other molecular alterations observed repeatedly in EBVaGC include (PD-L1) /PD-L2 amplification and mutations [34] in PIK3CA and ARID1A. In addition, EBV-encoded micrornas and long non-coding (lnc) RNAs have been implicated in tumorigenesis and progression [35]. EBV remains relevant in tumor maintenance and progression. Atsushi *et al.* [36] evaluated PD-L1 and tumor-infiltrating CD8+ T lymphocytes in EBV-positive and EBV-negative components to investigate how EBV loss in tumor cells affects the immune microenvironment, demonstrating that EBV induces an "immune fever" microenvironment that affects tumor maintenance.

3.2.2. Genomically Stable (GS) and Fusion Gene Drive

The fusion gene of CLDN18 (tight junction protein) and ARHGAP26 (Rho gtpase activating protein) is found in about 30% of gastric fundus and cardia cancers and is a prominent feature [37] of diffuse gastric cancer (DGC). This fusion results in aberrant binding of the transmembrane domain of CLDN18 to the catalytic domain of ARHGAP26, disrupting cell polarity and activating the RhoA signaling pathway. Studies have shown that ARHGAP26 originally inhibits signal transduction by catalyfying the conversion of RhoA-GTP to RhoA-GDP, but its GAP function is lost after fusion, leading to the continuous accumulation of RhoA-GTP and the activation of downstream effector molecules such as ROCK, which in turn enhances F-actin remodeling and cell migration [38]. In the organoid model, CLDN18-ARHGAP expression induced signet ring cell formation and synergistically promoted tumor transformation with TP53 deletion, as indicated by the activation of focal adhesion kinase (FAK) and YAP-TEAD pathways, which further drove invasive growth [39].

3.3. Pathogenesis of Gastric Body Cancer

The pathogenesis of gastric body cancer is between that of gastric antrum cancer and that of gastric fundus and cardia cancer. The uniqueness of gastric body cancer is mainly reflected in the fact that autoimmune gastritis is a specific subtype of chronic atrophic gastritis. Its characteristic pathological changes are progressive atrophy of the gastric body mucosa, and its core mechanism [40] involves the immune response mediated by autoantibodies against the H+/K+-ATPase and intrinsic factor of gastric parietal cells. This immune response leads to massive destruction of parietal cells and significant reduction of gastric acid secretion. Due to the absence of gastric acid, the negative feedback regulation mechanism fails and the compensatory proliferation of gastric antral G cells results in a significant increase in serum gastrin levels. The excess gastrin triggers the downstream mitogen-activated protein kinase (MAPK) signaling pathway by activating the cholecystokinin type 2 (CCK2) receptor. Abnormal activation of this pathway can induce the expression of cell proliferation-related genes, promote intestinal meta-

plasia and atypical hyperplasia of gastric mucosal glands, and ultimately increase the risk [41] of gastric body cancer. Epigenetic abnormalities also play a key role in the progression of gastric body cancer. Hypermethylation of the promoter region of CDH1 (encoding E-cadherin) leads to transcriptional silencing in up to 40% of gastric corpus adenocarcinoma, especially in signet ring cell subtype [42]. E-cadherin plays an important role in maintaining epithelial cell polarity and intercellular adhesion. The loss of E-cadherin function can lead to the destruction of cell-cell junction and the enhancement [43] of cell migration. This change is closely related to the diffuse infiltrative growth pattern and the tendency of peritoneal dissemination of signet ring cell carcinoma. This epigenetic change and the activation of MAPK pathway form a synergistic carcinogenic effect, which jointly promote the malignant transformation of gastric mucosa from chronic inflammation, metaplasia, dysplasia to invasive carcinoma.

4. Progress in Diagnosis and Treatment of Gastric Cancer

4.1. Innovation of Early Diagnosis Technology

Patients with newly diagnosed gastric cancer are usually found due to abnormal upper gastrointestinal endoscopy, and their chief complaints are mostly dyspepsia and reflux symptoms. However, some patients may present with symptoms or signs suggestive of advanced disease, such as dysphagia, weight loss, gastrointestinal bleeding, anemia, and vomiting [44]. Studies have shown that screening for gastric cancer can significantly reduce the mortality of this disease and improve the survival [45] rate of patients. Evidence from many countries and regions has shown that effective screening methods can be used for early [46] detection of gastric cancer. Screening methods for early gastric cancer usually include imaging examination, endoscopy, and biomarker detection. For imaging screening, a variety of methods can be used to detect gastric disease, such as upper gastrointestinal barium meal (UGI), multi-slice spiral CT, upper abdominal MRI, and gastric ultrasonography. Endoscopic techniques include white-light endoscopy, chromoendoscopy, and various computational virtual chromoendoscopy strategies, such as narrow-band imaging (NBI) and blue laser imaging (BLI), cytoendoscopy, confocal laser microendoscopy, and optical coherence tomography. In terms of biomarkers, in addition to the conventional markers commonly used in clinical practice (such as CEA, CA19-9 and CA72-4), some innovative biomarkers are also included. Such as peptides (PG, G-17, GCAA, TAA, etc.), DNA (cfDNA, DNA methylation, MSI), non-coding RNAs (miRNA, lncRNA, circRNA, and tsRNA), and circulating tumor cells [47].

4.2. Breakthroughs in Precision Treatment Strategies

4.2.1. Perioperative Chemotherapy Has Become the Standard Treatment for Resectable Gastroesophageal Adenocarcinoma

The MAGIC trial was the first to demonstrate that perioperative chemotherapy (ECF) significantly improved 5-year survival compared with surgery alone (36%

vs. 23%) [48]. FLOT4-AIO trial further optimized the regimen, and FLOT (fluorouracil + oxaliplatin + docetaxel) significantly prolonged the median OS (50 vs. 35 months) and 5-year OS rate (45% vs. 36%) compared with ECF, which became the new standard [49]. For HER2-positive patients, the PETRARCA trial showed that FLOT plus trastuzumab/pertuzumab improved the pCR rate (35% vs. 12%) and the node-negative rate (68% vs. 39%) [50].

4.2.2. Adjuvant Treatment Options

Postoperative adjuvant chemotherapy is recommended for patients with pT3/T4 or positive lymph nodes. The CLASSIC trial confirmed improved 3-year disease-free survival with capecitabine plus oxaliplatin (74% vs. 59%) [51]. In East Asian studies, S-1 alone or in combination with docetaxel (ACTS-GC and JACCRO GC-07 trials) significantly improved survival [52].

4.2.3. Treatment of Metastatic Gastric Cancer

First-line fluorouracil plus platinum regimens combined with nivolumab (PD-L1 CPS ≥ 5) or trastuzumab (HER2-positive) improved survival [53]. Paclitaxel plus ramucirumab was preferred as second-line therapy (OS 9.6 vs. 7.4 months), and trifluorouridine-tipiracil was optional as third-line therapy (OS 5.7 vs. 3.6 months) [54].

4.2.4. HER2-Targeted Progression

The ToGA trial established trastuzumab plus chemotherapy as the first-line treatment (OS 16.0 vs. 11.8 months). After resistance, trastuzumab deruxtecan showed an advantage in DESTINY-Gastric01 (OS 12.5 vs. 8.4 months) [55].

4.4. Critical Analysis of Diagnosis and Treatment Progress

Among the available diagnostic techniques, endoscopy has increased the detection rate of early gastric cancer to 90% by NBI combined with magnification, but the sensitivity for Borrmann type IV is only 60% [56]. Liquid biopsy can detect MSI status in ctDNA with a specificity of 85% in gastric body cancer but the sensitivity is limited by tumor [57] burden. Emerging multi-omics integration technologies can distinguish antrum and cardia cancer based on methylation profiling and proteomic typing. In terms of treatment strategy, Trastuzumab plus FLOT in HER2-positive antral cancer achieved a pCR rate of 35%, but the median PFS after resistance was only 5 months, while Trastuzumab deruxtecan still showed an ORR of 26% in HER2-low patients. In EBV+ gastric cardia cancer, the ORR of PD-L1 inhibitors in CPS ≥ 5 patients was 40%, but the response rate in negative patients was less than 15%. Cdh1-silenced gastric body cancer can reverse the expression of E-cadherin by HDAC inhibitors, but the clinical toxicity is significant [58]. It is necessary to combine single-cell sequencing to refine the subtyping and optimize resource allocation.

5. Conclusion

The clinicopathological and molecular characteristics of gastric cancer vary with

location. *Helicobacter pylori*-associated intestinal adenocarcinoma is the main type of gastric antrum cancer. CagA protein drives carcinogenesis by activating the Ras-Erk/β-catenin pathway, accompanied by TP53 mutation (50%) and HER2 amplification. Gastric cardia cancer is associated with metabolic syndrome and EBV infection. The characteristic CLDN18-ARHGAP fusion causes sustained activation of RhoA, and CpG island hypermethylation promotes invasion. Gastric body cancer is often accompanied by autoimmune gastritis. Apparent silencing of CDH1 and activation of MAPK pathway synergistically induce diffuse infiltration. Although the related research is deepening and developing, the specific mechanism is not fully understood. With the preparation of more and more basic experiments and the research of a large number of clinical data, it is believed that the treatment of gastric cancer will be more individualized and precise, and improve the global burden of disease in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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