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Emerging Genomic Biomarkers in Metastatic Gastric Cancer: Prognostic and Therapeutic Implications

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ABSTRACT

Background: Gastric cancer (GC) represents the fourth most prevalent malignancy globally and the second leading cause of cancer-related mortality. The anatomical location of gastric tumors significantly influences their pathological characteristics, with gastric antrum cancers typically manifesting as intestinal-type carcinomas associated with Helicobacter pyloriinfection, whereas fundus and cardia lesions more commonly exhibit diffuse-type histology.

Recent Advances: The integration of conventional tumor markers, including CEA and CA19-9, has demonstrated significant diagnostic utility. CA19-9 exhibits 56% sensitivity and 74% specificity for detecting recurrence, with sensitivity increasing to 87% when combined with CEA [3,4]. Molecular profiling has identified actionable genomic alterations, including HER2 amplification (15-20%), MSI-H (3-5%), and emerging targets such as CLDN18.2 (30-40%) and FGFR2b (5-10%).

Clinical Implications: The VIKTORY umbrella trial demonstrated that tumor genomic profiling can effectively guide targeted treatment selection in metastatic gastric cancer, establishing a paradigm for precision oncology. HER2-targeted therapy with trastuzumab, immune checkpoint inhibitors, and emerging agents targeting novel molecular pathways have transformed the therapeutic landscape.

Conclusion: The incorporation of genomic biomarkers into clinical practice enables personalized treatment approaches, improving patient selection and therapeutic outcomes in metastatic gastric cancer. Future directions include the integration of liquid biopsy technologies and comprehensive genomic profiling to advance precision oncology.

Keywords: Gastric cancer; metastatic disease; genomic biomarkers; HER2; precision medicine; tumor markers; liquid biopsy; immune checkpoint inhibitors; molecular profiling; prognostic factors**.**

INTRODUCTION

Gastric cancer (GC) ranks as the fourth most prevalent malignant condition and is the second most common cause of cancer-related mortality globally (Figure 1) (1). Despite considerable advancements in the survival rates of patients with gastric cancer (GC) during recent decades, GC is frequently detected at an advanced stage, and the prognosis remains unsatisfactory due to a high recurrence rate. Given that gastric cancer is predominantly asymptomatic until it reaches advanced stages, early detection using appropriate screening methods is crucial to reducing gastric cancer mortality rates. Biomarkers are objectively measurable qualities that serve as indicators of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions. Recent advancements in genomic research have identified several biomarkers associated with DNA, RNA, exosomes, and other entities (2). The advancement of these biomarkers in cancer treatment is anticipated to significantly enhance cancer progression, the selection of suitable therapeutic options, and the effectiveness of follow-up programs.

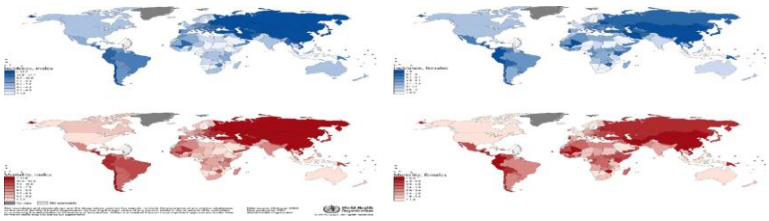

Figure 1 Global incidence and mortality rates of gastric cancer..

Biomarkers are biological molecules found in blood, fluids, or tissues that indicate normal or aberrant processes, illnesses, or diseases, including cancer; they may include proteins, nucleic acids, antibodies, peptides, and other substances. They can be categorized into prognostic biomarkers, which forecast cancer progression, and sensitivity-predictive biomarkers, which anticipate treatment response. The utilization of biomarkers holds promise in the formulation of novel anticancer drugs due to their numerous advantages, such as diminished toxicity, cost efficiency, and enhanced patient selection, which contribute to increased research and development success rates and reduced development expenses (3-5).

The advancement of molecularly targeted therapeutics has led to many clinical trial designs aimed at identifying patient subgroups most likely to benefit from these treatments. For instance, extensive randomized controlled trials assessing the efficacy of an intervention may incorporate the "enrichment" design, wherein "only biomarker-positive patients are included in the randomized controlled trial"; the "all-comers" design, in which "biomarkers are measured but all eligible patients are included in the randomized controlled trial irrespective of outcome"; and the hybrid design, where biomarkers are measured and positive patients are randomized to the study treatment group and the standard treatment group, while negative patients are allocated to the standard treatment group (6, 7).

The therapy of patients with metastatic gastric cancer remains a complex endeavor. No standardized first-line chemotherapy regimen exists; multiple acceptable regimens are available. First-line treatment typically comprises a fluoropyrimidine and a platinum-based agent. Nonetheless, certain regimens include irinotecan and taxanes in the initial treatment. Approximately 20% of individuals with gastric cancer have overexpression of the human epidermal growth factor receptor 2 (HER-2) (8). The use of trastuzumab into first-line, platinum-based chemotherapy for this patient cohort has enhanced survival rates (9). Checkpoint inhibitors have recently been incorporated into first-line treatment, leading to improved survival rates (10).

Etiology of Metastatic Gastric Cancer

Gastric cancer most commonly arises sporadically; however, approximately 5% to 10% of cases demonstrate a familial or inherited predisposition. A variety of environmental, infectious, host-related, and genetic factors contribute to its development (11, 12).

One of the most significant risk factors is chronic infection with *Helicobacter pylori*. Persistent or recurrent infection with this organism plays a central role in the development of gastric adenocarcinoma (1). The likelihood of malignancy is influenced by the duration of infection, coexisting environmental exposures, and individual host susceptibility. Another infectious agent increasingly linked to gastric cancer is Epstein–Barr virus (EBV), which is particularly associated with tumors arising in the proximal stomach (13).

Dietary habits also play an important role in gastric carcinogenesis. High salt intake, particularly from salt-preserved foods, and consumption of N-nitroso compounds increase risk. Diets low in vitamins A and C, along with high intake of smoked or cured foods, further contribute to susceptibility. Historically, a lack of refrigeration for food and contaminated drinking water have also been implicated. Lifestyle factors such as smoking significantly elevate the risk, especially among men, while obesity—reflected by a high body mass index—is strongly associated with cancers of the proximal stomach and the gastroesophageal junction (GEJ) (14, 15).

Chronic gastroesophageal reflux disease increases the incidence of adenocarcinoma at the GEJ. Additionally, bile reflux into the stomach, particularly following certain gastric surgeries, has been linked to a higher risk of malignancy. Occupational and environmental exposures, including work in rubber manufacturing, tin mining, metal processing, and coal industries, further heighten the risk (16).

Host-related factors also influence susceptibility. Individuals with blood group A have approximately a 20% higher incidence of gastric cancer compared with those of other blood groups, particularly for the diffuse type. Certain preexisting medical conditions significantly increased risk, including pernicious anemia and chronic atrophic gastritis, which may raise the likelihood of intestinal-type gastric cancer up to sixfold. Other associated conditions include benign gastric ulcers, hypertrophic gastropathy, and gastric polyps (17).

Conversely, some factors appear protective. Diets rich in fiber, fruits, and vegetables are associated with a reduced risk of gastric cancer, likely due to their antioxidant and anti-inflammatory effects (18).

A subset of gastric cancers occurs in the context of inherited cancer syndromes. Individuals with hereditary nonpolyposis colorectal cancer (Lynch syndrome) have an estimated 13% lifetime risk, predominantly of the intestinal type. Familial adenomatous polyposis carries an approximate 10% risk, while Peutz–Jeghers syndrome and juvenile polyposis syndrome are associated with lifetime risks of about 29% and 21%, respectively. Li-Fraumeni syndrome, hereditary breast and ovarian cancer syndrome, and Cowden syndrome (associated with PTEN mutations) are also linked to an increased risk of gastric cancer. Together, these genetic conditions underscore the importance of hereditary factors in a minority of cases (19, 20).

Table 1: A summary of the risk and protective factors for gastric cancer

Category	Risk / Factor	Key Details
Infectious Factors	*Helicobacter pylori*	Major risk factor for gastric adenocarcinoma; risk increases with chronic infection
	Epstein–Barr virus (EBV)	Associated mainly with proximal gastric cancer
Dietary Factors	High salt intake	Salt-preserved foods increase risk
	N-nitroso compounds	Carcinogenic compounds in certain preserved foods
	Smoked/cured foods	Increased risk with high consumption
	Low vitamins A & C	Reduced antioxidant protection
	Contaminated water/lack of refrigeration	Historical contributing factors
Lifestyle Factors	Smoking	Increased risk, especially in men
	Obesity	Higher risk of proximal gastric and GEJ cancers
Gastrointestinal Conditions	Chronic GERD	Associated with GEJ adenocarcinoma
	Bile reflux	Increased risk, especially post-gastric surgery
Environmental/Occupational	Industrial exposures	Rubber manufacturing, tin mining, metal processing, and coal industries
Host Factors	Blood group A	~20% higher incidence, especially diffuse type
	Pernicious anemia	Up to 6-fold increased risk (intestinal type)
	Chronic atrophic gastritis	Strong risk factor for intestinal type
	Gastric ulcers, hypertrophic gastropathy, gastric polyps	Associated increased risk
Genetic Syndromes	Lynch syndrome (HNPCC)	~13% lifetime risk (intestinal type)
	Familial adenomatous polyposis (FAP)	~10% risk
	Peutz–Jeghers syndrome	~29% risk
	Juvenile polyposis syndrome	~21% risk
	Li-Fraumeni syndrome	Associated with gastric cancer
	Hereditary breast & ovarian cancer	Increased risk

	Cowden (PTEN) syndrome	Associated with gastric cancer
Protective Factors	High fiber, fruits, vegetables	Likely protective effect

Pathophysiology of Metastatic Gastric Cancer

Gastric cancer exhibits distinct pathological and clinical features depending on its anatomical location. Gastric antrum cancer is typically an intestinal-type carcinoma associated with *Helicobacter pylori* infection. According to previous studies (21, 22), it is predominantly classified as the intestinal type under the Lauren system and as ulcerative (Borrmann types II and III) under the Borrmann classification. These tumors usually have well-defined margins and are frequently accompanied by mucosal atrophy and intestinal metaplasia. Histologically, about 70% of gastric antral cancers are well- to moderately differentiated tubular adenocarcinomas, characterized by highly differentiated cancer cells arranged in tubular formations. A small proportion are mucinous adenocarcinomas, which are associated with a poorer prognosis. Clinical guidelines indicate that early symptoms include dull epigastric pain and a sensation of fullness, often mistaken for chronic gastritis. In advanced stages, tumor invasion of the pylorus may cause gastric outlet obstruction, leading to vomiting and metabolic disturbances. Vascular invasion may result in melena or hematemesis. Metastasis most commonly occurs in the perigastric lymph nodes, while hematogenous spread is relatively uncommon (23, 24).

Gastric fundus and cardia cancers are generally diffuse-type gastric cancers and are often associated with metabolic disorders. Pathologically, they are characterized by diffuse infiltration and aggressive behavior (25). The typical Borrmann classification is type IV, known as “linitis plastica” or “leather stomach,” where tumor cells infiltrate the entire thickness of the gastric wall, causing rigidity and loss of peristalsis (26). The main histological types include signet ring cell carcinoma and poorly differentiated adenocarcinoma, with tumor cells infiltrating singly or in clusters and producing abundant mucin (27). Early symptoms, such as retrosternal burning and a sensation of a foreign body during swallowing, are frequently misdiagnosed as gastroesophageal reflux disease (GERD). As the disease progresses, patients often develop worsening dysphagia due to tumor invasion of the lower esophagus or cardiac sphincter. Peritoneal dissemination may lead to malignant ascites, indicating a very poor prognosis. Metastasis commonly involves mediastinal and celiac lymph nodes, as well as peritoneal spread (28).

Gastric body cancer represents a heterogeneous form of gastric cancer with a greater tendency for hematogenous dissemination. It may exhibit either intestinal or diffuse histological patterns, demonstrating marked pathological variability (29). Compared with antral cancer, diffuse-type adenocarcinoma is more prevalent in gastric body cancer, particularly among younger patients, and is associated with a worse prognosis. Intrinsic factor deficiency, leading to vitamin B12 malabsorption, is frequently observed. Hematogenous metastasis commonly involves the liver via the portal venous system (accounting for approximately 40% of cases), followed by metastases to the lungs and bones. Regarding lymphatic spread, metastasis to lymph nodes along the left gastric artery and at the splenic hilum is relatively common (30).

Genomic Biomarkers in Metastatic Gastric Cancer

Gastric tumor markers play important roles in diagnosis, staging, monitoring therapeutic response, and detecting recurrence after curative treatment (31). Although numerous biomarkers have been investigated for gastric cancer (GC)—including carbohydrate antigen (CA) 72-4, alpha-fetoprotein (AFP), CA125, SLE, BCA-225, human chorionic gonadotropin (hCG), and pepsinogen I/II—carcinoembryonic antigen (CEA) and CA19-9 remain the most commonly used markers in clinical practice (32, 33).

CEA

CEA is one of the most widely utilized tumor markers in digestive tract malignancies. It has been identified as an independent risk factor for predicting liver metastasis and recurrence (34, 35). Elevated CEA levels are typically observed in advanced-stage GC; however, because only a subset of patients show increased levels, CEA is not suitable as a screening tool. Measurement of CEA in peritoneal lavage fluid has been reported to accurately predict peritoneal recurrence following curative resection (32). Incorporating immunohistochemical CEA detection into conventional cytology improves diagnostic sensitivity. Furthermore, detection of CEA mRNA using RT-PCR is valuable for identifying peritoneal micrometastasis (36).

CA19-9

CA19-9 is a glycolipid antigen originally identified in colorectal cancer and serves as a ligand for E-selectin expressed on endothelial cells. Although commonly used in gastrointestinal cancers, it is particularly associated with pancreatic cancer and GC. CA19-9-positive GC tends to exhibit distinct clinicopathological features, including antral predominance, differentiated histology, marked lymphatic and venous invasion, increased lymph node metastasis, and advanced stage at diagnosis. Previous studies reported sensitivities of 56% and specificities of 74% for detecting recurrence (37-39). Combining CA19-9 with other tumor markers enhances predictive accuracy; for example, sensitivity increases to 87% when used together with CEA (38).

Other Conventional Biomarkers

Several additional tumor markers, including CA72-4, AFP, and CA125 have been applied in GC diagnosis. CA72-4 has been reported to offer higher sensitivity and accuracy than CEA in some studies, although data supporting its role in early detection or predictive screening remain limited (40, 41). AFP-positive GC is generally associated with advanced disease and a high incidence of liver metastasis. AFP-producing GC also demonstrates more aggressive tumor growth and increased neovascularization than AFP-negative tumors. Elevated CA125 levels have been strongly associated with peritoneal dissemination in GC, and CA125 positivity after curative surgery may predict peritoneal recurrence (42).

HER2

HER2 is the first molecular biomarker introduced into routine clinical practice for GC. Encoded by the ERBB2 gene on chromosome 17, HER2 is a transmembrane receptor tyrosine kinase and a member of the epidermal growth factor receptor (EGFR) family, which also includes EGFR/HER1, HER3, and HER4. Although its definitive prognostic and predictive value in GC remains under investigation, HER2 has emerged as an important therapeutic biomarker. HER2 amplification in GC has been reported in 6%–23% of cases, with overexpression more frequently observed in intestinal-type than diffuse-type tumors (32% vs. 6%) (8, 43).

Other HER2-targeted agents, including pertuzumab, lapatinib, and trastuzumab emtansine are currently under investigation in randomized clinical trials for HER2-positive GC, although definitive evidence of benefit remains limited. Challenges in advancing HER2-targeted therapy include optimizing trastuzumab dosing and identifying reliable predictive biomarkers (2, 44). Factors such as p27Kip1 expression and levels of the HER2 extracellular domain have shown potential utility in monitoring therapeutic efficacy.

Resistance to trastuzumab is an increasingly important issue in HER2-positive GC. One major mechanism involves dysregulation of the PI3K/Akt/mTOR signaling pathway. Mutations in PIK3CA and loss of PTEN function may reduce responsiveness to HER2-targeted therapy (38). Consequently, combining trastuzumab with PI3K inhibitors may provide clinical benefit. Additionally, CCNE1 amplification, one of the most common co-occurring genomic alterations has been negatively associated with response to HER2-directed therapy, suggesting its potential role as a biomarker of resistance in ERBB2-amplified GC (45). Other genomic biomarkers are depicted in Table 2.

Table 2 Genomic Biomarkers in Metastatic Gastric Cancer

Biomarker	Alteration Type	Frequency (Approx.)	Clinical Significance	Targeted Therapy
HER2 (ERBB2)	Gene amplification/overexpression	15–20%	Predicts response to anti-HER2 therapy	Trastuzumab ± chemotherapy; Trastuzumab deruxtecan
PD-L1 (CPS score)	Protein expression (IHC)	~40–60% (CPS ≥1)	Predicts benefit from immune checkpoint inhibitors	Nivolumab, Pembrolizumab
MSI-H / dMMR	Microsatellite instability/mismatch repair deficiency	~3–5% (metastatic)	Strong predictor of immunothe	Pembrolizumab, Nivolumab ± Ipilimumab

			rapy response	
EBV-positive tumors	EBV-associated molecular subtype	~8–10%	High PD-L1 expression; immunotherapy responsive	Immune checkpoint inhibitors
CLDN18.2	Protein overexpression	~30–40%	Targetable surface protein	Zolbetuximab + chemotherapy
FGFR2b	Gene amplification/overexpression	~5–10%	Emerging target	Bemarituzumab (investigational/region-dependent approval)
NTRK fusion	Gene fusion	<1%	Rare but actionable alteration	Larotrectinib, Entrectinib
MET amplification	Gene amplification	~2–4%	Potential therapeutic target	MET inhibitors (clinical trials)
KRAS amplification/mutation	Mutation/amplification	Variable (~5–10%)	May confer resistance to certain therapies	No standard targeted therapy yet
PIK3CA mutation	Gene mutation	~10–20%	More common in the EBV subtype	Investigational therapies

Therapeutic Options for treating Metastatic Gastric Cancer

The therapeutic landscape for metastatic gastric cancer has evolved substantially with the integration of molecularly targeted agents and immunotherapy. First-line treatment typically comprises a fluoropyrimidine and a platinum-based agent, though certain regimens incorporate irinotecan and taxanes in the initial treatment approach (46, 47).

Chemotherapy: Platinum-based combination regimens remain the cornerstone of systemic therapy for metastatic gastric cancer. The selection of specific agents depends on patient performance status, comorbidities, and molecular profiling results (46, 47).

HER2-Targeted Therapy: Approximately 20% of individuals with gastric cancer demonstrate overexpression of HER2. Trastuzumab, a monoclonal antibody targeting HER2, blocks HER2-mediated signaling and prevents cleavage of its extracellular domain. The Trastuzumab for Gastric Cancer (ToGA) trial demonstrated that adding trastuzumab to capecitabine or 5-FU plus cisplatin significantly improved tumor response compared with chemotherapy alone, establishing this combination as the standard of care for HER2-positive gastric cancer (46).

Immune Checkpoint Inhibitors: Checkpoint inhibitors have been incorporated into first-line treatment paradigms, leading to improved survival rates. Biomarkers such as PD-L1 CPS, MSI-H status, and EBV positivity guide patient selection for immunotherapy (47, 48). Patients with MSI-H tumors demonstrate particularly robust responses to immune checkpoint blockade.

Genomics-Guided Treatment: The VIKTORY umbrella trial represents a landmark study demonstrating that

tumor genomic profiling can effectively guide patients with metastatic gastric cancer to targeted treatment. This trial established a framework for precision oncology in gastric cancer by matching patients with specific genomic alterations to corresponding targeted therapies (49). Emerging targets include CLDN18.2, FGFR2b, and NTRK fusions, expanding the therapeutic armamentarium for molecularly selected patient subgroups (48, 50).

CONCLUSION

The integration of genomic biomarkers into the management of metastatic gastric cancer has transformed clinical practice, enabling personalized treatment approaches based on molecular profiling. Conventional tumor markers, including CEA and CA19-9, retain important roles in disease monitoring and recurrence detection. The emergence of actionable molecular targets, including HER2, PD-L1, MSI-H, CLDN18.2, and FGFR2b, has expanded therapeutic options and improved outcomes for selected patient populations.

The VIKTORY trial paradigm demonstrates the feasibility and clinical utility of genomics-guided treatment selection. As our understanding of gastric cancer biology continues to evolve, the incorporation of comprehensive genomic profiling into routine clinical practice will be essential for optimizing patient care and advancing precision oncology in this challenging malignancy.

Future Perspectives

The future of metastatic gastric cancer management lies in the continued refinement of precision medicine approaches. Emerging genomic profiling technologies, including next-generation sequencing and circulating tumor DNA analysis, promise to enhance our ability to identify actionable alterations and monitor treatment response in real-time (50, 51). Liquid biopsy approaches offer the potential for non-invasive serial monitoring of molecular evolution and resistance mechanisms (51).

The development of novel predictive biomarkers will further refine patient selection for targeted therapies and immunotherapy. Ongoing research into the tumor microenvironment, immune landscape, and resistance mechanisms will inform the development of rational combination strategies (47, 48). The integration of functional precision medicine approaches, which combine genomic profiling with ex vivo drug sensitivity testing, may further enhance treatment selection and overcome the limitations of genotype-directed therapy alone (52).

International collaborative efforts and basket/umbrella trial designs will accelerate the identification and validation of novel therapeutic targets. As the therapeutic armamentarium continues to expand, biomarker-driven treatment algorithms will become increasingly sophisticated, offering the promise of improved outcomes for patients with metastatic gastric cancer (47, 49).

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