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Gastric Cancer: Challenges in New Era Treatment Strategy

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Abstract

Gastric cancer (GC) remains a significant global health burden and is among the leading causes of cancer-related mortality worldwide. Although the overall incidence has declined in some regions due to improved hygiene and Helicobacter pylori eradication, GC continues to present major clinical challenges, largely because of late-stage diagnosis, tumour heterogeneity, and limited accessibility to advanced therapeutic options. Over the past five years, significant advances have been achieved in understanding the molecular pathogenesis of GC, identifying novel biomarkers, and refining both early detection and treatment strategies. Recent studies highlight the importance of molecular classification systems, including microsatellite instability, Epstein–Barr virus-associated tumours, and genomically stable versus chromosomal instability subtypes, which have crucial implications for prognosis and personalized therapy. Innovations in endoscopic screening, imaging modalities, and liquid biopsy approaches have enhanced diagnostic accuracy and facilitated earlier intervention. Therapeutically, there has been a shift toward integrating targeted therapies, immunotherapy, and perioperative chemotherapy, improving outcomes in both localized and metastatic disease. Despite these advances, challenges remain in overcoming therapy resistance, addressing disparities in healthcare access, and translating molecular insights into routine clinical practice. This narrative review synthesizes

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contemporary evidence from 2019 to 2024, drawing on 20 high-quality studies and systematic reviews, to provide a comprehensive overview of epidemiology, risk factors, molecular mechanisms, diagnostic strategies, current and emerging therapeutic approaches, and future research directions in GC. By consolidating these findings, this review aims to inform clinicians, researchers, and policymakers about the evolving landscape of gastric cancer management and to identify key areas where further investigation and innovation are required.

Keywords: Gastric cancer, molecular classification, targeted therapy, immunotherapy, early diagnosis

INTRODUCTION

Gastric cancer (GC) represents a complex, multifactorial malignancy with considerable variation in incidence, mortality, and clinical presentation across geographic regions and socioeconomic groups (1,4,6). Although global incidence has declined over recent decadesmainly due to improved sanitation, reduced *Helicobacter pylori* prevalence, and dietary changes, GC remains highly prevalent in East Asia, Eastern Europe, and parts of Latin America, continuing to pose a major public health challenge (1–4,6). Environmental exposures, lifestyle factors, and host genetics contribute to disease heterogeneity, complicating early detection, risk stratification, and treatment strategies (7–9). Consequently, tailored prevention programs and region-specific screening strategies are essential to reduce disease burden (6,15,16).

Of growing concern is the rising incidence of early-onset GC among younger adults, a trend associated with more aggressive histopathology, delayed diagnosis, and poorer prognosis compared to conventional GC (5,6,9). Genetic predispositions, including hereditary diffuse gastric cancer (HDGC), play a prominent role in this subgroup, highlighting the importance of molecular and familial risk assessment (5,9). Current research emphasizes the need for targeted surveillance and age-specific management protocols, aiming to improve outcomes in younger populations while addressing the increasing clinical burden of early-onset disease (5,6,12).

Recent advances in molecular profiling, endoscopic techniques, and systemic therapies have significantly reshaped the management of GC (2,3,10–13). Molecular classifications—such as microsatellite instability, Epstein–Barr virus-associated tumours, and chromosomal instability provide critical prognostic information and guide personalized therapeutic approaches (10–12,18–20). Innovations in diagnostic endoscopy and imaging enable earlier detection, while multimodal treatment strategies, including perioperative chemotherapy (e.g., FLOT regimen), HER2-targeted therapy, and immunotherapy combinations, have improved outcomes for both localized and metastatic disease (13,17–20,23). Despite these advancements, prognosis for advanced GC remains suboptimal, underscoring the ongoing need for novel biomarkers, precision medicine approaches, and optimized screening interventions (21,22). This review aims to provide an updated, comprehensive synthesis of recent literature, focusing on epidemiology, molecular insights, diagnostic strategies, and evolving therapeutic paradigms in GC (2,3,5).

Gastric cancer (GC) remains a major global health concern, ranking among the leading causes of cancer-related mortality, with over one million new cases diagnosed annually (1,4). The burden

of disease is unequally distributed, with East Asian countries, particularly Japan and South Korea, exhibiting the highest incidence rates (4–6). Despite high incidence, these countries report some of the best survival outcomes globally, largely attributable to long-standing, population-based screening programs that enable early detection and timely intervention (4,15). In contrast, many Western and low- to middle-income countries continue to face late-stage diagnoses and poorer survival, reflecting disparities in healthcare access, screening uptake, and early detection strategies (4,6,16).

Recent epidemiological data indicate a concerning rise in GC incidence among adults under 50 years of age, often presenting as diffuse-type tumours with aggressive histopathological and molecular features (5,6). This trend of early-onset GC differs from traditional late-onset disease, both in biological behaviour and clinical outcomes, and is prompting investigations into hereditary syndromes, environmental exposures, and lifestyle-related risk factors (5,9). Early-onset GC frequently exhibits rapid progression and a higher propensity for metastasis, underscoring the urgent need for tailored risk stratification and surveillance strategies for younger populations (5,6,12).

The shifting epidemiology of GC highlights the importance of integrating demographic trends, molecular insights, and regional variations into public health planning and clinical practice (4–6). Risk-adapted screening programs, particularly in high-incidence areas, have proven effective in improving early detection and long-term survival, whereas low-incidence regions may benefit from targeted screening based on individualized risk assessment (15,16). Understanding global patterns and evolving demographic shifts is essential for optimizing resource allocation, designing effective preventive strategies, and guiding research priorities aimed at reducing the worldwide burden of gastric cancer (4–6).

METHODOLOGY

This narrative literature review was conducted to provide a comprehensive and integrative overview of current knowledge on gastric cancer, with particular emphasis on epidemiology, pathogenesis, molecular classification, diagnostic strategies, therapeutic advances, and public-health perspectives. Given the broad and evolving nature of the topic, a narrative review approach was selected to allow critical synthesis of heterogeneous evidence, including epidemiologic studies, clinical trials, translational research, and authoritative reviews.

Literature Search Strategy

A structured literature search was performed using major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science. The search covered publications from January 2019 to March 2025, ensuring inclusion of the most recent evidence reflecting contemporary clinical practice and research

developments. Key search terms and Medical Subject Headings (MeSH) were combined using Boolean operators and included: "gastric cancer," "stomach neoplasms," "epidemiology," "Helicobacter pylori," "molecular classification," "TCGA," "diagnosis," "endoscopy," "gastrectomy," "perioperative chemotherapy," "targeted therapy," "immunotherapy," "screening," and "early detection." Reference lists of relevant articles were also manually screened to identify additional influential studies not captured by the initial search.

Eligibility Criteria

Included publications comprised narrative and systematic reviews, randomized controlled trials, large observational studies, meta-analyses, clinical practice guidelines, and key position papers published in peer-reviewed journals. Priority was given to studies addressing adult gastric cancer, contemporary diagnostic or therapeutic strategies, and molecular or immunologic insights with clinical relevance. Articles focusing exclusively on paediatric populations, non-gastric upper gastrointestinal malignancies, or outdated therapeutic approaches were excluded unless they provided essential historical or conceptual context.

Study Selection and Data Extraction

The initial database search yielded a total of **87 records**. After removal of duplicates and screening of titles and abstracts, **64 articles** were excluded due to lack of relevance to the review objectives. Full-text assessment was subsequently performed on the remaining **23 studies**, all of which were included in the qualitative synthesis of this review.

Data extraction focused on key thematic domains: epidemiologic trends, risk factors and prevention, molecular subtypes, clinical presentation and staging, histopathology, diagnostic innovations, surgical and systemic treatment strategies, immunotherapy outcomes, screening approaches, and survivorship issues.

Synthesis Approach

Given the narrative nature of the review, evidence was synthesized thematically rather than statistically. Emphasis was placed on integrating findings across disciplines to reflect the multidisciplinary management of gastric cancer. Landmark trials, major epidemiologic analyses, and high-impact reviews were highlighted to contextualize evolving standards of care. Areas of inconsistency or controversy were discussed to identify knowledge gaps and future research directions. This approach aimed to provide a balanced and clinically meaningful synthesis rather than an exhaustive enumeration of all available studies.

LITERATURE REVIEW

Risk Factors and Pathogenesis

The development of gastric cancer (GC) is driven

by a complex interplay of environmental, infectious, genetic, and epigenetic factors (7–9). Among these, *Helicobacter pylori* infection remains the predominant risk factor for non-cardia GC, acting through the well-characterized Correa cascade, which progresses from chronic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately carcinoma (7,8). Population-based studies consistently demonstrate that effective eradication of *H. pylori* significantly reduces GC incidence, highlighting the central role of this pathogen in gastric carcinogenesis (7).

Beyond *H. pylori*, additional environmental and lifestyle factors contribute to GC pathogenesis. Autoimmune gastritis, Epstein–Barr virus (EBV) infection, dietary exposure to nitrosamines, tobacco smoking, obesity, and alterations in the gastric microbiome have all been implicated in promoting malignant transformation (7,8). These factors may act synergistically or independently to induce chronic inflammation, DNA damage, and epigenetic modifications, thereby facilitating tumour initiation and progression (8). The contribution of diet and microbiota emphasizes the potential for preventive interventions, including lifestyle modification and microbiome-targeted strategies, particularly in high-risk populations (8).

Genetic predisposition also plays a critical role in a subset of GC cases. Hereditary syndromes, including CDH1-related hereditary diffuse gastric cancer (HDGC) and Lynch syndrome, account for a smaller proportion of patients but carry significant clinical implications (9). Carriers of pathogenic variants often present with early-onset, aggressive disease and require comprehensive genetic counselling, rigorous surveillance, and in some cases, prophylactic surgical interventions (9). Integrating knowledge of hereditary syndromes with environmental and infectious risk factors is essential for personalized prevention strategies and optimizing patient outcomes in both familial and sporadic GC (7–9). The multistep pathogenesis of gastric cancer is summarized in Figure 1 and involves a complex interaction between environmental exposures, Helicobacter pylori–induced chronic inflammation, and molecular alterations.

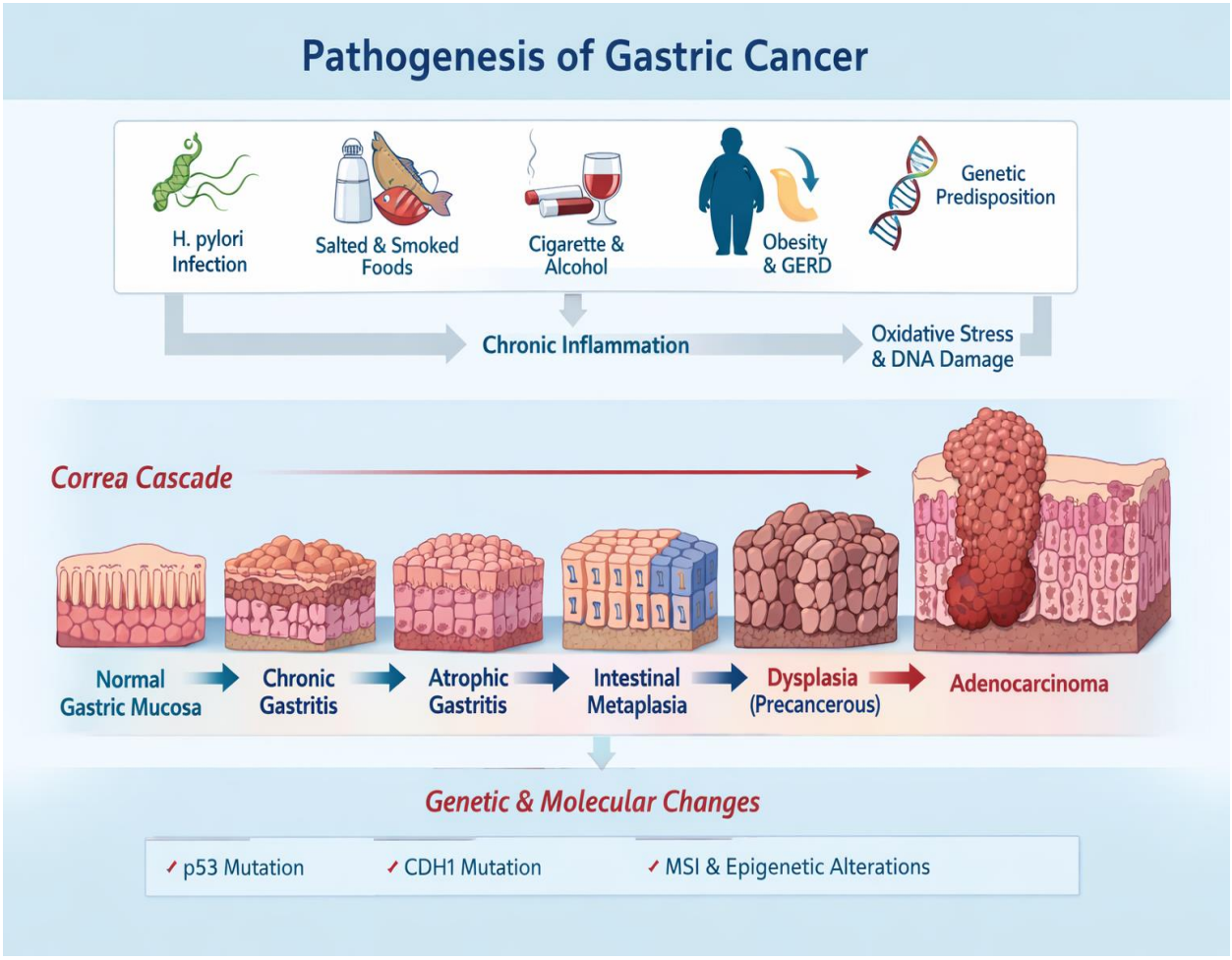

Figure 1. Pathogenesis of gastric cancer.

This schematic illustration summarizes the multistep pathogenic mechanisms involved in gastric cancer development, including major environmental and infectious risk factors, Helicobacter pylori–induced chronic inflammation, progression through the Correa cascade (chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia), and key molecular and genetic alterations leading to invasive carcinoma. Source: *Author's own illustration, created for this review and based on published literature (1–4).*

Molecular Classification

Advances in genomic profiling have significantly enhanced the understanding of gastric cancer (GC) biology, enabling the identification of distinct molecular subtypes with prognostic and therapeutic relevance (10–12). The Cancer Genome Atlas (TCGA) framework categorizes GC into four major subtypes: Epstein–Barr virus (EBV) positive, microsatellite instability (MSI), genomically stable (GS), and chromosomal instability (CIN) (10). Each subtype exhibits unique molecular characteristics, clinical behaviour, and therapeutic susceptibilities, highlighting the importance of molecular

stratification in guiding personalized management strategies (10–12).

In clinical practice, MSI-high and EBV-positive tumours have garnered particular attention due to their increased responsiveness to immune checkpoint inhibitors, marking a paradigm shift in the use of immunotherapy for GC (10–12,23). Furthermore, actionable biomarkers such as HER2 amplification, FGFR2 alterations, CLDN18.2 expression, and PD-L1 status have become integral to therapeutic decision-making, enabling the selection of targeted agents and combination therapies (11,12,18–20). These molecular insights facilitate precision oncology approaches, optimizing treatment efficacy while minimizing unnecessary toxicity.

Recent multi-omics studies have continued to refine GC taxonomy, revealing additional molecular clusters with potential prognostic and therapeutic implications (10–12). Integration of genomic, transcriptomic, and proteomic data is enhancing the ability to predict treatment response, identify novel drug targets, and better understand tumor heterogeneity. As molecular profiling becomes increasingly accessible in routine clinical practice, these advances are expected to guide the next generation of personalized therapies, improve survival outcomes, and inform the design of future clinical trials (11,12).

Clinical Presentation and Diagnosis

Gastric cancer (GC) often remains asymptomatic in its early stages, contributing to delayed diagnosis and poor prognosis, particularly in regions without established screening programs (13,15,16). When symptoms do occur, they are frequently nonspecific and may include epigastric pain, unintended weight loss, anaemia, early satiety, nausea, or dyspepsia. This subtle presentation underscores the critical importance of high clinical suspicion and timely diagnostic evaluation, especially in high-risk populations (13,15).

Endoscopy with systematic biopsy continues to be the gold-standard diagnostic modality for GC, allowing direct visualization and histopathological confirmation (13). Recent technological advancements in endoscopic imagingsuch as narrow-band imaging, confocal laser endomicroscopy, and artificial intelligenceassisted detection algorithmshave enhanced the sensitivity and specificity for identifying early lesions and premalignant changes (13). Complementary imaging modalities, including cross-sectional techniques (CT, MRI), endoscopic ultrasound, and diagnostic laparoscopy, play essential roles in tumor staging, detection of regional lymph node involvement, and identification of occult peritoneal metastases (14).

Current guidelines recommend the routine incorporation of molecular testing at diagnosis to guide individualized treatment strategies (12–14,18–20). Key biomarkers, including HER2 amplification, PD-L1 expression, microsatellite instability (MSI), and CLDN18.2 expression, inform decisions regarding targeted therapies, immunotherapy, and eligibility for clinical trials (12,18–20). Integration of molecular profiling with advanced imaging and endoscopic techniques provides a comprehensive framework for accurate diagnosis, precise staging, and personalized management, ultimately aiming to improve survival outcomes in patients with GC (13,14).

The diagnostic evaluation of gastric cancer is multifaceted, combining clinical assessment with endoscopic examination, imaging studies, histopathology, and molecular profiling to ensure accurate staging and guide treatment selection (Figure 2). Early identification of tumor location, depth of invasion, and metastatic spread is essential for optimizing therapeutic outcomes.

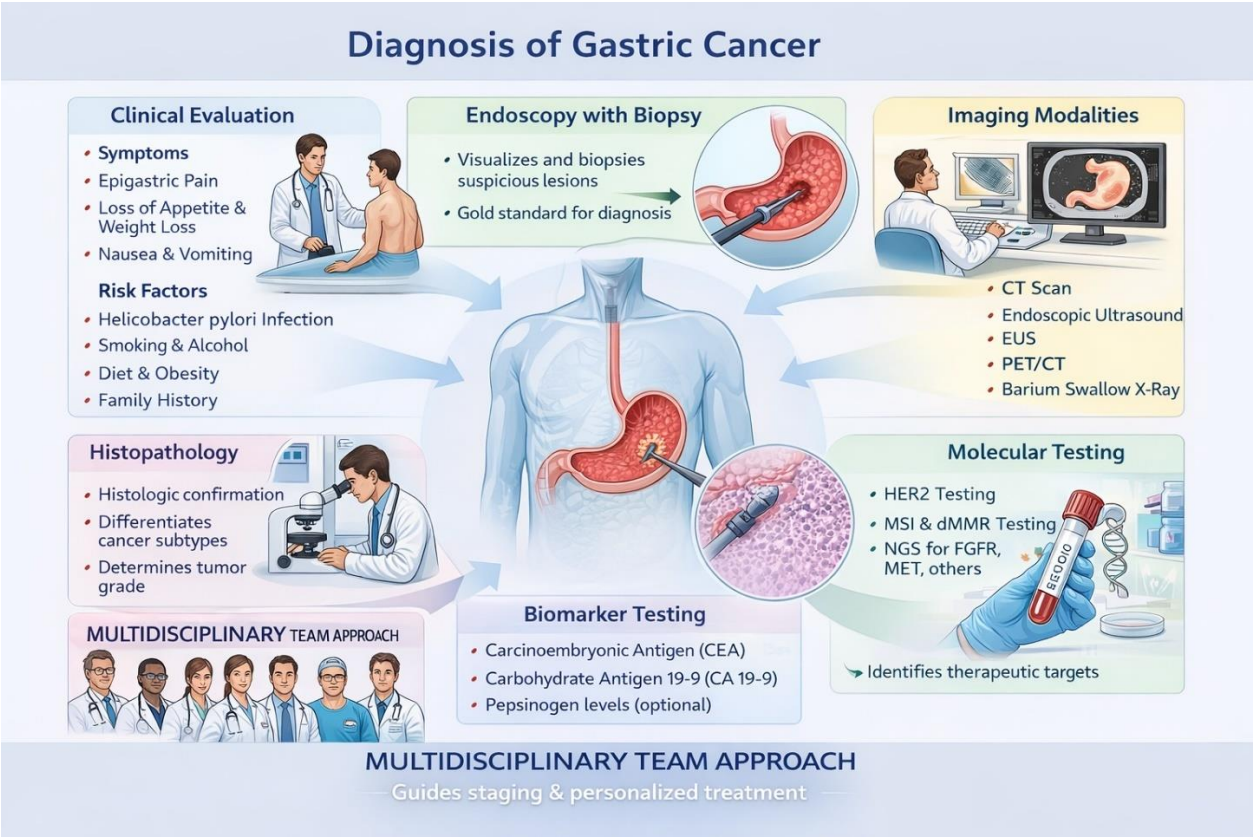

Figure 2. Diagnostic pathway of gastric cancer, integrating clinical evaluation, endoscopy, imaging, histopathology, and molecular profiling. Source: *Author's own illustration, created for this review and based on published literature (20-21).*

Screening and Early Detection

Population-based screening programs in Japan and South Korea represent global models of success in gastric cancer (GC) early detection, utilizing endoscopy and radiography to identify premalignant and early-stage lesions (15). These programs have substantially improved survival outcomes, demonstrating the critical impact of systematic surveillance in high-incidence regions. The long-standing implementation of such programs highlights the benefits of early diagnosis and provides a framework for other countries aiming to reduce GC mortality (15).

Recent research has focused on refining screening strategies through risk-based algorithms that integrate *Helicobacter pylori* infection status, serum pepsinogen levels, genomic risk signatures, and artificial intelligence driven predictive models (15,16). These approaches aim to optimize resource allocation by targeting individuals at highest risk while maintaining sensitivity for early lesion detection. Cost-effectiveness analyses in Europe and the United States suggest that selective, risk-adapted screening may be feasible in low- to intermediate-incidence populations, although additional evidence is needed to guide widespread implementation (16).

The last five years have also seen growing interest in non-invasive biomarkers, including circulating tumor DNA (ctDNA) and microRNAs, which hold promise for complementing existing screening methods and enabling earlier detection of GC (22). Integration of these emerging molecular tools with traditional endoscopic and imaging strategies may further enhance early diagnosis, risk stratification, and timely therapeutic intervention. Ongoing studies are expected to clarify the clinical utility of these biomarkers and support the development of personalized, population-tailored screening programs (15,16,22).

Treatment Strategies

Early-stage Disease

Early gastric cancer (GC) can be effectively managed with endoscopic resection techniques, particularly endoscopic submucosal dissection (ESD), when strict criteria regarding lesion size, depth of invasion, and lymph-node risk are met (17). For patients with surgically resectable disease, gastrectomy with D2 lymphadenectomy remains the global standard, offering excellent oncologic outcomes. Minimally invasive approaches, including laparoscopic and robotic gastrectomy, have demonstrated comparable efficacy while providing advantages such as reduced postoperative pain, faster recovery, and shorter hospital stays (17). In Western practice, perioperative chemotherapymost notably the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) has become the preferred standard for enhancing survival in locally advanced resectable disease (17).

Locally Advanced Disease

For locally advanced GC, multimodal therapy is essential to improve outcomes. Randomized trials

consistently support perioperative chemotherapy as the backbone of treatment, often combined with surgery and radiation in select cases (17,18). Precision oncology approaches are increasingly integrated into the treatment paradigm, including HER2-targeted agents, CLDN18.2-directed therapy (zolbetuximab), FGFR2 inhibitors, and immunotherapy. Early introduction of these targeted and immune-based therapies, guided by molecular profiling, allows for more personalized treatment strategies and the potential for improved survival (18,20).

Metastatic Disease

Therapeutic advances in metastatic GC have been substantial over the last five years. Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, have demonstrated meaningful clinical benefits in PD-L1 positive, MSI-high, and EBV-positive tumours (19,23). HER2-positive GC now benefits from trastuzumab-based combinations, as well as next-generation agents like trastuzumab deruxtecan, which have shown superior efficacy in phase II/III trials (19). Additionally, targeted therapies against CLDN18.2 (zolbetuximab) and FGFR2b (bemarituzumab) represent major breakthroughs, offering improved survival outcomes in carefully selected patient populations (20). Multimodal strategies combining chemotherapy, immunotherapy, and targeted therapies are increasingly employed to optimize response, highlighting the growing role of precision oncology in metastatic GC management (19,20,23).

Prognosis

Overall survival in gastric cancer (GC) remains limited, particularly in patients with advanced or metastatic disease, with five-year survival rates generally below 40% in most Western countries (21). Prognosis is strongly influenced by several factors, including stage at diagnosis, molecular subtype, access to multimodal treatment, and response to systemic therapies (21). Early-stage disease detected through screening programs or incidental findings typically carries a favorable prognosis, whereas late-stage presentation remains a major contributor to poor outcomes globally (15,16,21).

Molecular characteristics play an increasingly important role in predicting treatment response and survival. Tumors with microsatellite instability (MSI-high), Epstein–Barr virus (EBV) positivity, and HER2 amplification are associated with improved outcomes when matched with appropriate targeted therapies or immunotherapy (12,18–20,21). Conversely, genomically stable and chromosomal instability subtypes often present therapeutic challenges and are linked to poorer prognosis (10–12).

Surgical resection with negative margins (R0 resection) remains the most critical prognostic determinant in operable GC, underscoring the importance of accurate staging, careful surgical planning, and integration of perioperative or

adjuvant therapies (17,21). Emerging biomarkers, including circulating tumor DNA (ctDNA), may offer additional prognostic insights and help guide post-treatment surveillance strategies (22). Collectively, these factors highlight the multifaceted nature of GC prognosis and the need for individualized, precision-based management approaches to improve patient outcomes (21,22).

Future Directions

Emerging research in gastric cancer (GC) is increasingly focused on refining molecular classification and leveraging these insights to guide personalized therapy (10–12,22). The integration of artificial intelligence (AI) into endoscopic and pathological workflows promises to enhance early detection, improve diagnostic accuracy, and facilitate real-time risk stratification (13,15,16). Biomarker-driven therapies continue to expand, with ongoing studies evaluating novel targets such as CLDN18.2, FGFR2, and immune checkpoint pathways, aiming to optimize therapeutic response and minimize toxicity (18–20,23).

Circulating tumor DNA (ctDNA) has garnered significant attention as a tool for detecting minimal residual disease, monitoring treatment response, and identifying early relapse, offering the potential for real-time, non-invasive patient management (22). Multi-omics approaches, combining genomic, transcriptomic, and proteomic analyses, along with microbiome-based therapeutic strategies, are further refining our understanding of tumor heterogeneity and identifying novel intervention points (11,12,22). These strategies hold promise for personalizing treatment, predicting outcomes, and overcoming resistance mechanisms.

Ongoing clinical trials exploring combinations of immunotherapy, targeted therapy, and chemotherapy continue to reshape the therapeutic landscape for GC, particularly in advanced and metastatic disease (19,20,23). Future progress is likely to emerge from the integration of precision oncology with population-based preventive strategies, including risk-adapted screening and early detection programs (15,16,22). Collectively, these advances emphasize a shift toward individualized, biology-driven management approaches that aim to improve survival, reduce recurrence, and optimize quality of life for patients with GC (22,23).

DISCUSSION

Gastric cancer (GC) remains a major public health concern worldwide, owing to its high incidence, complex aetiology, and frequent late-stage diagnosis (1–6). Although global incidence has declined over the past decades due to improved sanitation, reduced *Helicobacter pylori* prevalence, and dietary changes, East Asia, Eastern Europe, and parts of Latin America continue to bear the highest burden (4–6). Population-based screening programs in Japan and South Korea have demonstrated that early detection significantly improves survival outcomes, highlighting the critical impact of

organized surveillance in high-risk populations (15). Conversely, in many Western countries, late-stage presentation persists, emphasizing the need for risk-adapted screening strategies that account for demographic shifts, including the rising incidence of early-onset GC (5,6,15,16).

The pathogenesis of GC is multifactorial, integrating environmental exposures, infectious agents, genetic predisposition, and epigenetic alterations (7–9). *H. pylori* infection remains the primary driver of non-cardia GC, progressing through the well-characterized Correa cascade from chronic gastritis to carcinoma (7). Additional contributors, such as autoimmune gastritis, EBV infection, dietary nitrosamines, smoking, obesity, and perturbations in the gastric microbiome, further modulate risk (7,8). Hereditary syndromes, including CDH1-related hereditary diffuse gastric cancer (HDGC) and Lynch syndrome, although relatively rare, are clinically significant and necessitate genetic counselling and preventive interventions (9). These insights underscore the importance of a holistic approach to risk assessment that considers both modifiable and non-modifiable factors.

Advances in molecular classification have transformed the clinical landscape, providing a framework for personalized management (10–12). The TCGA molecular subtypes: EBV-positive, microsatellite instability-high (MSI-H), genomically stable (GS), and chromosomal instability (CIN)have prognostic and therapeutic implications, particularly as MSI-H and EBV-positive tumours show enhanced responsiveness to immunotherapy (10–12). Actionable biomarkers such as HER2 amplification, CLDN18.2 expression, FGFR2 alterations, and PD-L1 status increasingly guide treatment decisions (18–20). Multi-omics approaches continue to reveal novel molecular clusters, offering the potential for more precise patient stratification and individualized therapy (11,12).

Diagnostic and therapeutic innovations have significantly improved the management of GC. Endoscopic advancements, including narrow-band imaging, confocal laser endomicroscopy, and artificial intelligence-assisted detection algorithms, have increased sensitivity for early lesions, while imaging modalities such as CT, MRI, endoscopic ultrasound, and diagnostic laparoscopy remain critical for accurate staging (13–14). Perioperative chemotherapy regimens, particularly the FLOT protocol, minimally invasive gastrectomy techniques, and targeted agents including trastuzumab, trastuzumab deruxtecan, zolbetuximab, and FGFR2 inhibitors have expanded therapeutic options (17–20). Furthermore, immunotherapy has reshaped the treatment paradigm for advanced disease, especially in PD-L1 positive, MSI-H, or EBV-positive tumors, supporting a multimodal, precision-based approach (19,20,23).

Despite these advancements, challenges persist in translating scientific progress into widespread clinical benefit. Limitations include inequitable access to advanced therapies, variability in screening program implementation, and the need

for further validation of emerging biomarkers such as circulating tumor DNA (ctDNA) and microRNAs (15,16,22). Integrating molecular profiling with population-level preventive strategies, along with the use of AI-assisted diagnostics and multi-omics analyses, offers a promising pathway to improve early detection, personalize therapy, and enhance survival (11,12,15,16,22,23). Future research should focus on refining predictive models, exploring novel therapeutic targets, and establishing collaborative frameworks that bridge precision oncology with public health initiatives, ultimately reducing the global burden of GC.

CONCLUSION

Gastric cancer remains a major global health challenge, with high morbidity and mortality, particularly in regions with limited screening and late-stage diagnosis (1–4,6). Recent advances in molecular profiling, targeted therapies, immunotherapy, and minimally invasive diagnostic techniques have substantially improved the management of both early-stage and advanced disease (10–12,13–20,22,23). Population-based screening and early detection remain crucial for improving survival, while integration of genomic insights and biomarker-driven strategies enables personalized therapy (15,16,18–20,22,23).

Future efforts should focus on expanding risk-adapted screening programs, promoting access to novel therapeutic agents, and incorporating emerging biomarkers and AI-assisted diagnostic tools into clinical practice. The combination of precision oncology with population-level preventive strategies holds the potential to reduce gastric cancer mortality, optimize patient outcomes, and guide research priorities for the coming years (22,23).

RECOMMENDATIONS

To further improve outcomes, it is recommended to expand risk-adapted screening programs in high- and intermediate-incidence regions, integrate molecular profiling into routine clinical practice, and promote access to novel targeted and immunotherapeutic agents (15,16,18–20). Investment in research on emerging biomarkers, AI-assisted diagnostics, and multi-omics approaches should be prioritized to enable early detection, personalize therapy, and guide clinical decision-making. Collaborative efforts combining precision medicine, population health strategies, and patient-centered care are essential for reducing the global burden of gastric cancer and improving long-term survival (22,23).

Limitations

As a narrative review, this work does not follow the formal protocol or reproducibility standards of a systematic review, and selection bias cannot be entirely excluded. Nevertheless, by prioritizing recent, high-quality, and widely cited literature, the review seeks to present an accurate and current representation of the field. The focus on English-language publications may also limit

inclusion of relevant data from non-English sources.

Ethical Considerations

This study is based exclusively on previously published data and did not involve human participants or identifiable patient information; therefore, ethical approval was not required.

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Conflict of Interest Statement: The authors declare that they have no conflict of interest.

REFERENCES

1. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2021;71(3), 209–249. https://doi.org/10.3322/caac.21660.

2. Smyth EC, Nilsson M, Grabsch HI et al. Gastric cancer. The Lancet 2020;396(10251), 635–648. https://doi.org/10.1016/S0140-6736(20)31288-5.

3. Ajani JA, D'Amico TA, Bentrem DJ et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network 2022;20(2), 167–192. https://doi.org/10.6004/jnccn.2022.0008.

4. Arnold M, Abnet CC, Neale RE et al. Global burden of 5 major types of gastrointestinal cancer. Gut 2020;69(2), 335–344. https://doi.org/10.1136/gutjnl-2019-318243.

5. Kato K, Yamada T. Trends in early-onset gastric cancer. Gastroenterology 2023;164(1), 20–23. https://doi.org/10.1053/j.gastro.2022.09.045.

6. Lee JH, Kim YI, Kim JH. Gastric cancer epidemiology in Korea and worldwide. The Lancet Gastroenterology & Hepatology 2022;7(10), 890–902. https://doi.org/10.1016/S2468-1253(22)00217-4.

7. Correa P, Piazuelo MB. Gastric cancer: Overview. Nature Reviews Gastroenterology & Hepatology 2021;18(10), 629–644. https://doi.org/10.1038/s41575-021-00444-1.

8. Yoon H, Kim N, Park JH. The role of gastric microbiota in gastric carcinogenesis. Gut and Liver 2020;14(2), 187–196. https://doi.org/10.5009/gnl19041.

9. van der Post RS, Vogelaar IP, Carneiro F et al. Hereditary diffuse gastric cancer: Updated clinical guidelines. The Lancet Oncology 2021;22(12), e386–e397. https://doi.org/10.1016/S1470-2045(21)00526-0.

10. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513(7517), 202–209. https://doi.org/10.1038/nature13480.

11. Wang Q, Yu J, Zhang X. Multi-omics approaches in gastric cancer. Frontiers in Oncology 2022;12, 876543.

https://doi.org/10.3389/fonc.2022.876543.

12. Liu Y, Sethi NS, Lee S. Molecular classification of gastric cancer. Cancers 2023;15(3), 722. https://doi.org/10.3390/cancers15030722.

13. Ono H, Yao K, Fujishiro M et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Digestive Endoscopy 2020;32(4), 497–514. https://doi.org/10.1111/den.13507.

14. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2021 (6th ed.). Gastric Cancer 2021;24(1), 1–21. https://doi.org/10.1007/s10120-020-01042-y.

15. Choi IJ, Kim CG, Lee JY et al. Family history of gastric cancer and Helicobacter pylori treatment. The New England Journal of Medicine 2020;382(5), 427–436. https://doi.org/10.1056/NEJMoa1909666.

16. Gupta S, Li D, El-Serag HB, Davila JA. Risk-based gastric cancer screening in Western populations. Clinical Gastroenterology and Hepatology 2022;20(1), 34–44. https://doi.org/10.1016/j.cgh.2021.01.032.

17. Al-Batran SE, Homann N, Pauligk C et al. Perioperative chemotherapy with FLOT versus ECF/ECX. The Lancet 2019;393(10184), 1948–1957. https://doi.org/10.1016/S0140-6736(18)32557-1.

18. Shitara K, Bang YJ, Iwasa S et al. Trastuzumab deruxtecan in HER2-positive gastric cancer. The New England Journal of Medicine 2022;386(25), 2419–2430. https://doi.org/10.1056/NEJMoa2112433.

19. Janjigian YY, Kawazoe A, Yanez P et al. Pembrolizumab plus chemotherapy in advanced gastric cancer. The New England Journal of Medicine 2023;388(11), 1011–1024. https://doi.org/10.1056/NEJMoa2209641.

20. Sahin U, Türeci Ö, Manikhas G et al. Zolbetuximab plus chemotherapy for CLDN18.2-positive gastric cancer. The New England Journal of Medicine 2023;388(12), 1091–1102. https://doi.org/10.1056/NEJMoa2300484.

21. Markar SR, Karthikesalingam A, Thrumurthy S, Møller H. Volume–outcome relationship in gastric cancer surgery. British Journal of Surgery 2021;108(2), 123–132. https://doi.org/10.1093/bjs/znaa098.

22. Maron SB, Chase LM, Lomnicki S et al. Circulating tumor DNA analysis in advanced gastric cancer. Clinical Cancer Research 2023;29(3), 590–600. https://doi.org/10.1158/1078-0432.CCR-22-2051.

23. Peters S, Adjei AA, Gridelli C et al. Immunotherapy combinations in solid tumors. Annals of Oncology 2024;35(1), 1–13. https://doi.org/10.1016/j.annonc.2023.10.001.