Immunohistochemistry in Gastric Carcinoma: Diagnostic Subtyping, Prognostic Stratification, and Predictive Biomarkers

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Abstract

Background: Background: Gastric carcinoma remains a major cause of cancer-related mortality worldwide, largely because many patients present at advanced stage and because the disease comprises biologically diverse tumor entities with different pathways of carcinogenesis and treatment responsiveness. While histomorphology remains the foundation for diagnosis and classification, it does not fully capture the molecular heterogeneity of gastric cancer or reliably predict prognosis and therapeutic benefit. In this context, immunohistochemistry (IHC) has become an essential component of contemporary gastric cancer pathology. IHC supports accurate diagnostic subtyping in limited biopsy material, assists in resolving challenging differentials, and offers practical surrogates for molecular alterations that have direct clinical implications. The modern era of gastric cancer management increasingly relies on integrated pathology reporting that combines morphology with biomarkers relevant to risk assessment, stratification of patients, and selection of targeted or immune-based therapies.

Aim: This review summarizes the evidence-based role of immunohistochemistry in gastric carcinoma with emphasis on three major domains: (1) diagnostic subtyping and problem-solving in routine surgical pathology, (2) prognostic stratification through immunophenotypic and tumor microenvironment profiling, and (3) predictive biomarker assessment that guides therapeutic decision-making. The review also highlights key technical considerations, interpretation pitfalls, and the clinical value of structured IHC-based algorithms in both biopsy and resection specimens.

Conclusion: Immunohistochemistry is central to the modern pathological evaluation of gastric carcinoma, enabling clinically meaningful classification beyond morphology alone. When applied thoughtfully and interpreted in conjunction with histologic context and awareness of pre-analytical and biological variability, IHC improves diagnostic confidence, refines prognostic assessment, and identifies predictive biomarker-defined subgroups that may benefit from precision therapies. A standardized, evidence-based approach to marker selection and reporting—linked to molecular subtypes and treatment pathways—strengthens the role of pathology in multidisciplinary gastric cancer care and supports individualized patient management.

Keywords: Immunohistochemistry, Gastric Carcinoma, Biomarkers

Introduction

Gastric carcinoma remains one of the most important malignancies worldwide, representing a major cause of cancer-related morbidity and mortality. Despite a gradual decline in incidence over recent decades, gastric cancer is currently ranked as the fifth most frequently diagnosed malignancy and the fourth leading cause of cancer-related death globally, underscoring its aggressive nature and poor overall prognosis [1,2]. The high mortality rate is largely attributable to late-stage diagnosis, marked biological heterogeneity, and limited effectiveness of conventional therapeutic strategies in advanced disease [3]. The global distribution of gastric carcinoma demonstrates striking geographic variability. The highest incidence rates are observed in East Asia, particularly in Japan, Korea, and China, followed by Eastern Europe and parts of Latin America, which together account for more than 60% of global cases [2,4]. In contrast, gastric cancer is relatively uncommon in Africa and North America. Nevertheless, survival outcomes differ markedly between regions; for example, Japan reports five-year survival rates exceeding 90% due to population-based screening and early detection programs, whereas survival in many Western countries remains below 30% [1,5]. These disparities highlight the critical role of early diagnosis and optimized pathological assessment in improving patient outcomes.

Gastric carcinoma is a multifactorial disease arising from a complex interaction between environmental exposures, infectious agents, and host-related genetic susceptibility. Established environmental and lifestyle-related risk factors include *Helicobacter pylori* infection, high dietary salt intake, consumption of processed and smoked foods, tobacco smoking, alcohol use, and obesity [3,6]. Among these, *H. pylori* infection represents the most significant etiological factor and has been classified as a class I carcinogen by the World Health Organization. It is implicated in approximately 80–90% of non-cardia gastric carcinomas worldwide through the induction of chronic inflammation and progressive mucosal damage [7,8].

From a pathological standpoint, gastric carcinogenesis is widely understood as a stepwise process involving well-defined precursor lesions. This progression, commonly described as the Correa cascade, begins with chronic gastritis and advances through chronic atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately invasive adenocarcinoma [9,10]. Accurate identification and grading of these premalignant lesions are central to risk stratification, surveillance strategies, and cancer prevention. However, significant histological overlap and interobserver variability persist, particularly in small biopsy specimens, limiting the reliability of morphology alone in clinical decision-making [10,11].

Histologically, gastric carcinoma encompasses a broad spectrum of morphologic patterns that reflect underlying biological diversity. The Lauren classification remains widely used, dividing tumors into intestinal, diffuse, and mixed types, each associated with distinct etiologic pathways, molecular alterations, and clinical behavior [12]. Complementing this system, the World Health Organization classification provides a more detailed histological framework, incorporating poorly cohesive carcinoma, mucinous adenocarcinoma, and several rare variants with unique prognostic and therapeutic implications [13]. While histomorphology remains the cornerstone of diagnosis, it is increasingly evident that morphology alone is insufficient to capture the biological complexity of gastric cancer.

Advances in molecular pathology have further refined the understanding of gastric carcinoma heterogeneity. Large-scale genomic studies have identified reproducible molecular subtypes with distinct clinicopathological features, prognostic implications, and therapeutic relevance. These molecular classifications have emphasized the importance of integrating traditional histopathology with ancillary testing to provide clinically actionable information [14,15]. However, comprehensive molecular testing is not universally available and may be limited by cost, infrastructure, and tissue availability.

In this context, immunohistochemistry (IHC) has emerged as an indispensable tool in routine gastric

cancer pathology. IHC provides practical, widely accessible surrogates for underlying molecular alterations and plays a critical role in diagnostic subtyping, prognostic stratification, and predictive biomarker assessment. It aids in resolving morphologically ambiguous cases, supports tumor classification in limited biopsy material, and identifies clinically relevant subgroups that may benefit from targeted or immune-based therapies [16,17]. Moreover, IHC allows evaluation of tumor differentiation, proliferative activity, and features of the tumor microenvironment, all of which contribute to risk assessment and therapeutic planning.

Despite its widespread use, the application of immunohistochemistry in gastric carcinoma is associated with several challenges, including tumor heterogeneity, variability in staining protocols, lack of universal scoring systems for certain biomarkers, and discrepancies between biopsy and resection specimens [16]. These limitations underscore the need for an evidence-based, pathology-oriented framework for IHC marker selection and interpretation.

Accordingly, this review aims to comprehensively evaluate the role of immunohistochemistry in gastric carcinoma, focusing on its utility in diagnostic subtyping, prognostic stratification, and predictive biomarker identification. By synthesizing current evidence from the literature and integrating histopathological, immunophenotypic, and molecular perspectives, this article seeks to provide a practical reference for pathologists and clinicians involved in the multidisciplinary management of gastric cancer.

Normal Gastric Histology and Epithelial Homeostasis: Pathological Foundations for Immunohistochemical Interpretation

Accurate interpretation of immunohistochemical findings in gastric carcinoma requires a solid understanding of normal gastric anatomy, histology, and epithelial differentiation. The stomach is anatomically divided into the cardia, fundus, body (corpus), antrum, and pylorus, each characterized by distinct glandular compositions and cellular lineages [18,19]. These regional differences are not only relevant for routine histopathological evaluation but also critically influence immunophenotypic expression patterns observed in both non-neoplastic and neoplastic gastric tissues.

Histologically, the gastric mucosa is composed of surface foveolar epithelium and underlying glands embedded within the lamina propria. In the fundus and corpus, oxyntic glands predominate and contain parietal cells, chief cells, mucous neck cells, and scattered enteroendocrine cells, whereas the antral mucosa is characterized by mucous glands with fewer parietal and chief cells [18–20]. These normal cellular constituents exhibit distinct immunohistochemical profiles, which must be recognized to avoid misinterpretation when evaluating gastric biopsies, particularly in the context of atrophic or metaplastic change.

Gastric epithelial homeostasis is maintained through a tightly regulated process of cellular renewal driven by stem and progenitor cell populations located primarily within the isthmus and neck regions of the gastric glands [21,22]. These stem cells give rise to multiple epithelial lineages that migrate bidirectionally toward the surface epithelium or deeper glandular compartments. Disruption of this regenerative balance, often through chronic inflammation or genetic alterations, contributes to aberrant differentiation patterns that can be detected immunohistochemically and may precede overt neoplastic transformation [21].

From a pathological perspective, chronic injury to the gastric mucosa—most commonly mediated by *Helicobacter pylori* infection or autoimmune mechanisms—leads to progressive architectural distortion and loss of specialized glandular cells [23,24]. This process culminates in chronic atrophic gastritis, a recognized precursor condition for gastric carcinoma. Histologically, atrophic gastritis is characterized by glandular loss, replacement by fibrous tissue or metaplastic epithelium, and variable inflammatory infiltrates, all of which alter the baseline immunophenotype of the gastric mucosa [25].

Intestinal metaplasia represents a critical intermediate stage in gastric carcinogenesis and is defined by the replacement of native gastric epithelium with intestinal-type cells expressing absorptive, goblet, and Paneth cell differentiation [26]. This metaplastic transformation is of particular importance to pathologists because it introduces immunohistochemical expression patterns that resemble intestinal epithelium,

potentially confounding the interpretation of tumor origin and differentiation in biopsy material [27]. Subclassification of intestinal metaplasia into complete and incomplete types has prognostic significance, with incomplete metaplasia associated with a higher risk of progression to dysplasia and carcinoma [28]. Dysplasia of the gastric epithelium represents the final preinvasive stage in the multistep model of gastric carcinogenesis. It is characterized by cytologic atypia, architectural complexity, and loss of normal maturation. From an immunohistochemical standpoint, dysplastic lesions often show altered expression of markers related to proliferation, differentiation, and cellular polarity, changes that may overlap with those observed in early invasive carcinoma [29,30]. This overlap underscores the importance of correlating immunohistochemical findings with architectural and cytologic features rather than relying on biomarker expression in isolation.

Understanding normal gastric histology and its spectrum of non-neoplastic alterations is therefore essential for the rational application of immunohistochemistry in gastric carcinoma. Baseline knowledge of regional glandular differentiation, stem cell dynamics, and precursor lesion morphology provides the necessary framework for interpreting immunophenotypic changes associated with neoplastic transformation. Without this foundation, immunohistochemical results risk being misapplied or overinterpreted, particularly in limited biopsy specimens and inflamed or atrophic mucosa.
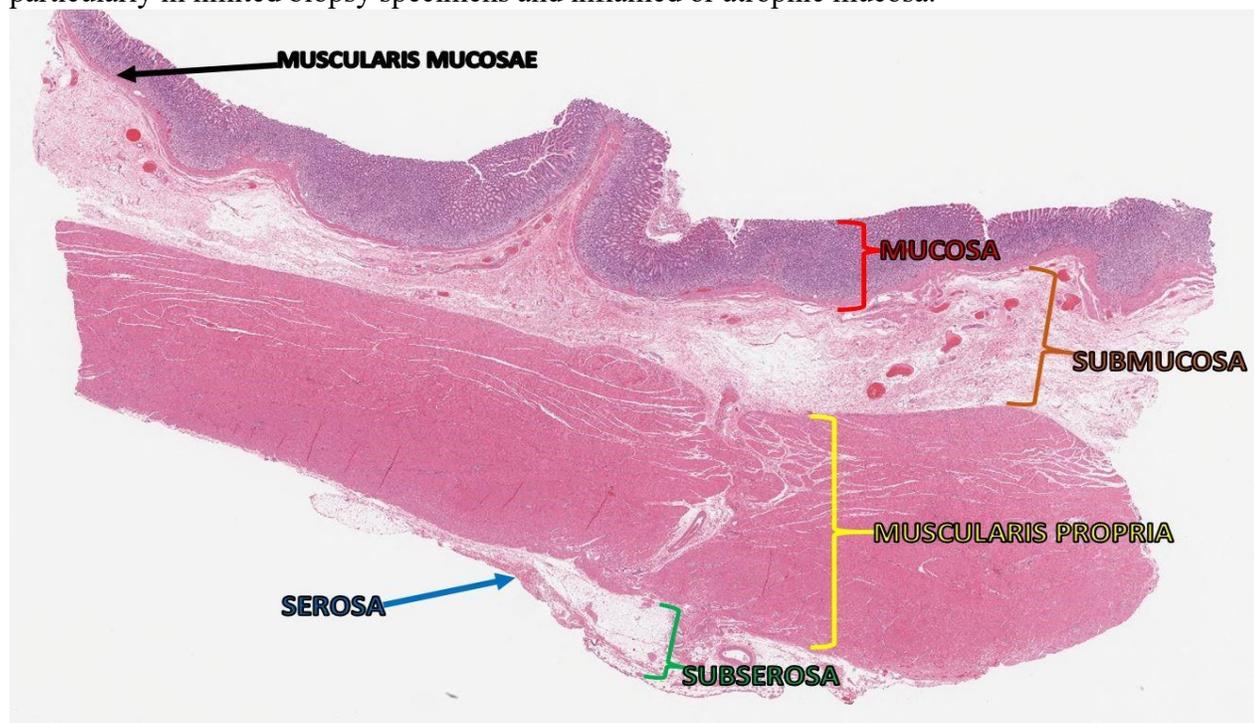

Figure 1: Normal gastric wall showing mucosa, submucosa, muscularis propria, and serosa. Adapted from McHugh KE, Pathology Outlines, 2025.
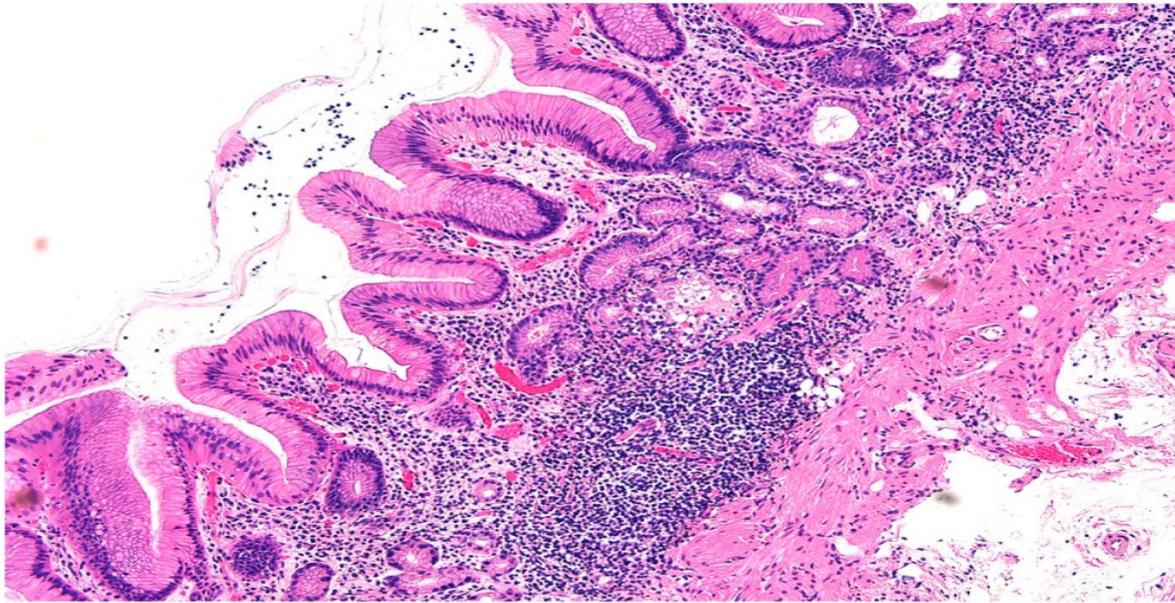
Figure2: Histopathological image of AIG. Lymphocytic infiltration is seen in the deep layer of the lamina propria retrieved from Wang et al.,2021
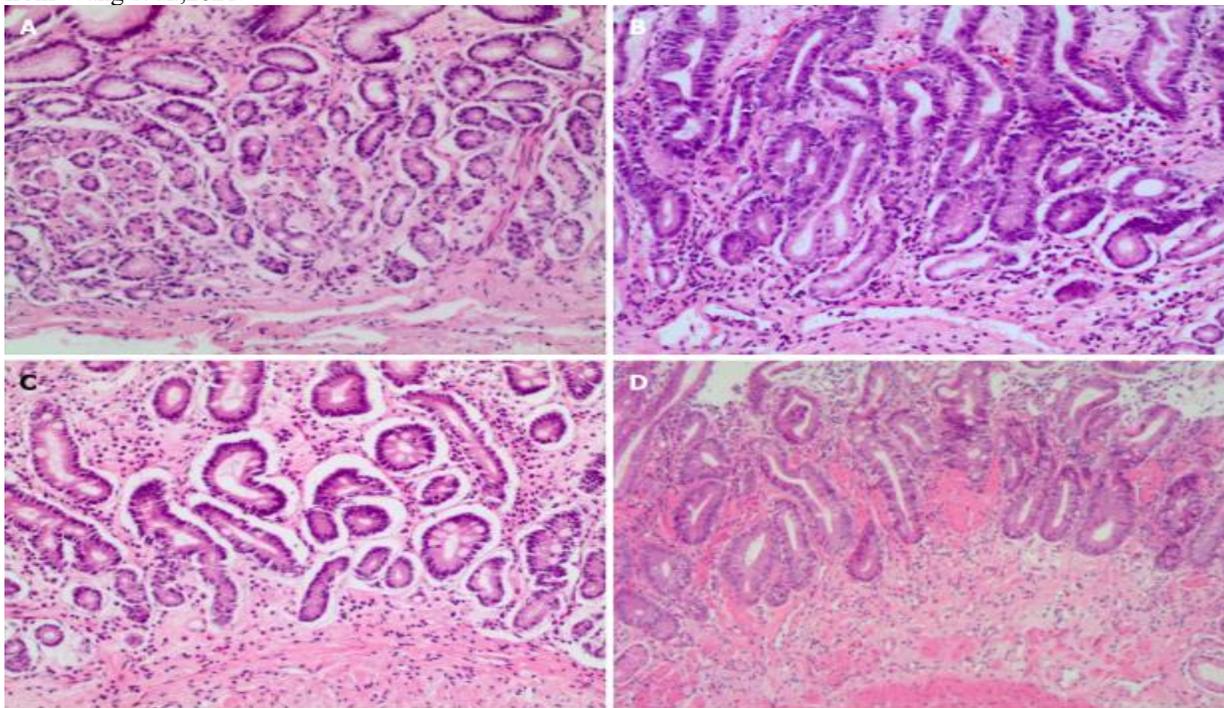

Fig3: A: Simple type chronic atrophic gastritis—only thinning mucosal and gland atrophy, no glandular hyperplasia or heterotypic and intestinal metaplasia. B: Hyperplasia type chronic atrophic gastritis—inherent layer atrophy accompanied by glandular hyperplasia, mainly quantitative, with no epithelial atypical hyperplasia. C: Intestinal metaplasia type chronic atrophic gastritis—intrinsic glandular atrophy accompanied by intestinal metaplasia, mainly small intestinal epithelial metaplasia. D: Intraepithelial neoplasia type chronic atrophic gastritis—inherent layer atrophy with high grade intraepithelial neoplasia retrieved from Wang et al.,2021
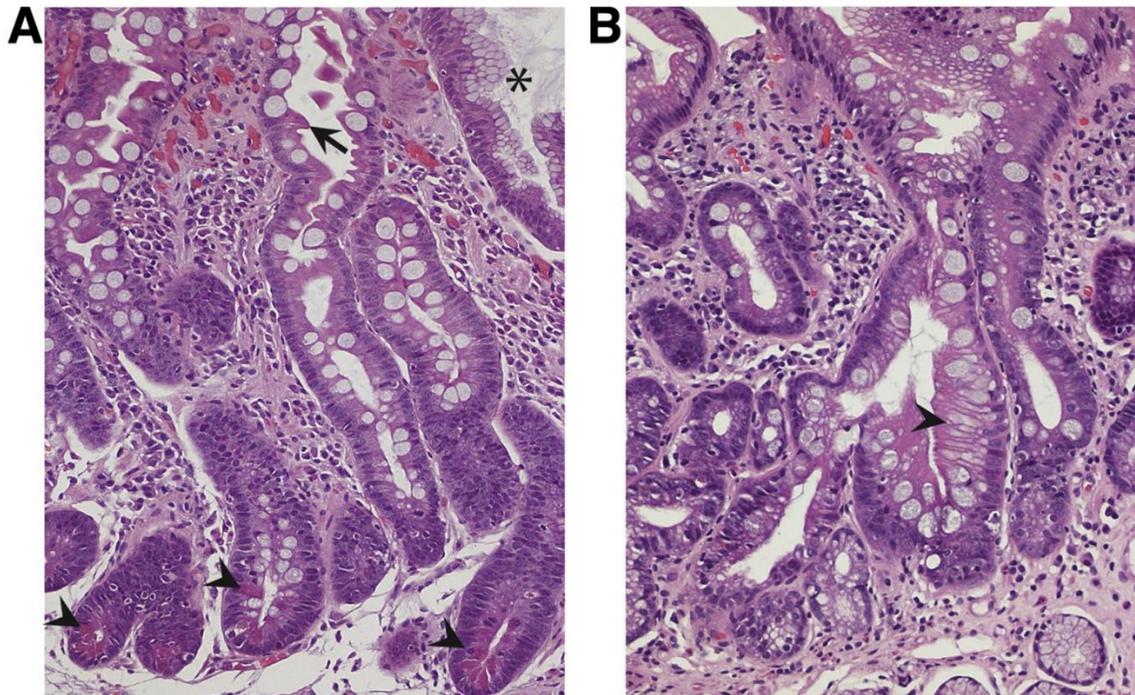
Figure 4:(A) GIM, complete type, with straight crypt architecture, well-developed goblet cells, eosinophilic enterocytes with brush border (*arrow*), and Paneth cells at the crypt base (*arrowheads*). Wang et al.,2021

Gastric Carcinoma Classification: Morphologic and Molecular Context for Immunohistochemistry

Gastric carcinoma represents a heterogeneous group of malignant epithelial tumors with diverse histological appearances, biological behaviors, and clinical outcomes. Accurate classification is therefore fundamental to diagnosis, prognostication, and therapeutic decision-making. Traditionally, gastric carcinoma classification has relied on histomorphological assessment, which remains the cornerstone of pathological evaluation. However, advances in molecular pathology have revealed substantial heterogeneity within morphologically defined categories, emphasizing the need for integrated classification systems that combine morphology with immunohistochemical and molecular features [31,32].

The Lauren classification remains one of the most widely used histological systems and divides gastric carcinoma into intestinal, diffuse, and mixed types. Intestinal-type gastric carcinoma is characterized by gland-forming architecture resembling intestinal epithelium and is commonly associated with chronic gastritis, intestinal metaplasia, and environmental risk factors. In contrast, diffuse-type carcinoma is composed of poorly cohesive cells, often including signet ring cells, and lacks glandular formation. This subtype is frequently associated with genetic susceptibility and demonstrates more aggressive behavior with early infiltration and poor prognosis [33,34]. Mixed-type carcinomas exhibit overlapping features of both categories and further illustrate the biological continuum of gastric cancer.

While the Lauren system provides valuable clinicopathological correlations, it does not fully capture the diversity of gastric carcinoma subtypes encountered in routine practice. The World Health Organization (WHO) classification offers a more detailed histological framework, recognizing tubular, papillary, mucinous, and poorly cohesive carcinomas, as well as several rare variants such as gastric carcinoma with lymphoid stroma, hepatoid adenocarcinoma, adenosquamous carcinoma, and fundic gland–type adenocarcinoma [35,36]. These entities differ markedly in prognosis and molecular characteristics,

underscoring the importance of precise histological categorization.

From a prognostic standpoint, certain histological subtypes are associated with distinct clinical outcomes. Poorly cohesive carcinoma, particularly when enriched in signet ring cells, is often associated with advanced stage at presentation, peritoneal dissemination, and resistance to conventional chemotherapy [37,38]. Conversely, gastric carcinoma with lymphoid stroma, frequently associated with Epstein–Barr virus infection, tends to exhibit a more favorable prognosis and distinct immune-rich tumor microenvironment [39,40]. Recognition of these subtypes has direct implications for patient stratification and therapeutic planning.

Large-scale molecular studies have further refined gastric carcinoma classification. The Cancer Genome Atlas (TCGA) identified four major molecular subtypes: Epstein–Barr virus–positive tumors, microsatellite instability (MSI) tumors, genomically stable tumors, and chromosomal instability tumors [41]. Independently, the Asian Cancer Research Group (ACRG) proposed a related but distinct molecular classification that also demonstrated strong prognostic associations [42]. These molecular frameworks have highlighted biological pathways underlying tumor behavior, including immune activation, DNA repair deficiency, epithelial–mesenchymal transition, and chromosomal instability.

Importantly, these molecular subtypes show partial but incomplete overlap with traditional histological classifications. For example, diffuse-type carcinomas are frequently associated with the genomically stable subtype, whereas intestinal-type tumors are more often linked to chromosomal instability [41–43]. This imperfect concordance reinforces the limitations of morphology alone and supports the use of ancillary techniques, particularly immunohistochemistry, to bridge histological and molecular classification systems.

Immunohistochemistry plays a critical intermediary role between morphology and molecular profiling. It enables identification of molecularly defined subgroups using surrogate markers that are widely available in routine pathology laboratories. Through targeted immunohistochemical panels, pathologists can approximate molecular subtypes, assess tumor differentiation pathways, and provide clinically actionable information even when comprehensive genomic testing is not feasible [44,45]. Thus, immunohistochemistry serves as a practical extension of classification systems, translating complex molecular insights into everyday diagnostic practice.

In summary, gastric carcinoma classification has evolved from purely morphologic systems to multidimensional frameworks incorporating molecular and immunophenotypic data. Understanding the strengths and limitations of each classification approach is essential for the rational application of immunohistochemistry. In the following sections, the diagnostic, prognostic, and predictive roles of immunohistochemistry in gastric carcinoma will be discussed in detail within this integrated classification context.
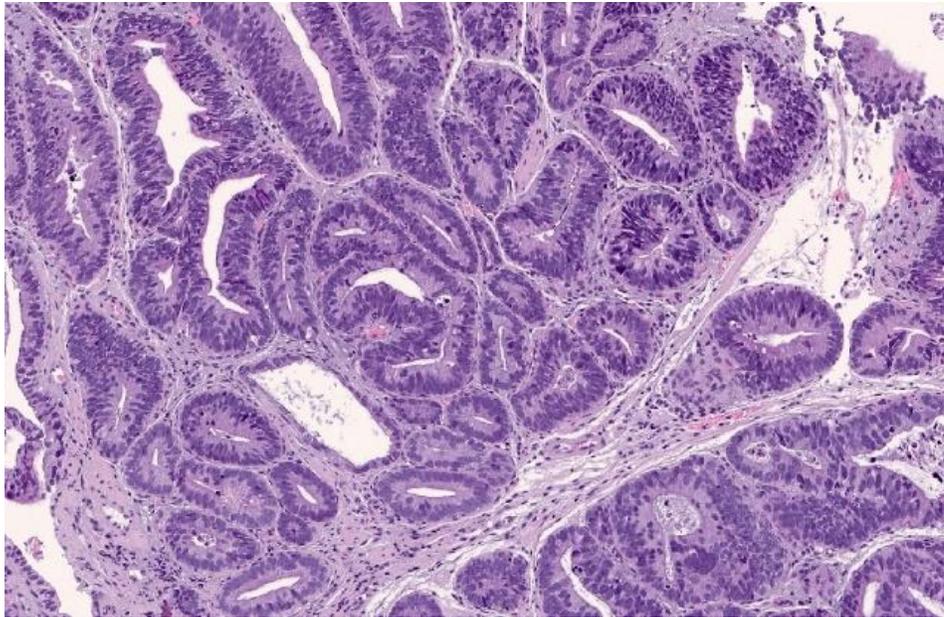
Figure 5: Intestinal type gastric carcinoma (Neoplastic proliferation composed of epithelial cells with intestinal appearance forming glands. It corresponds to the well differentiated tubular subtype of the WHO classification *(Martínez,2025)*.
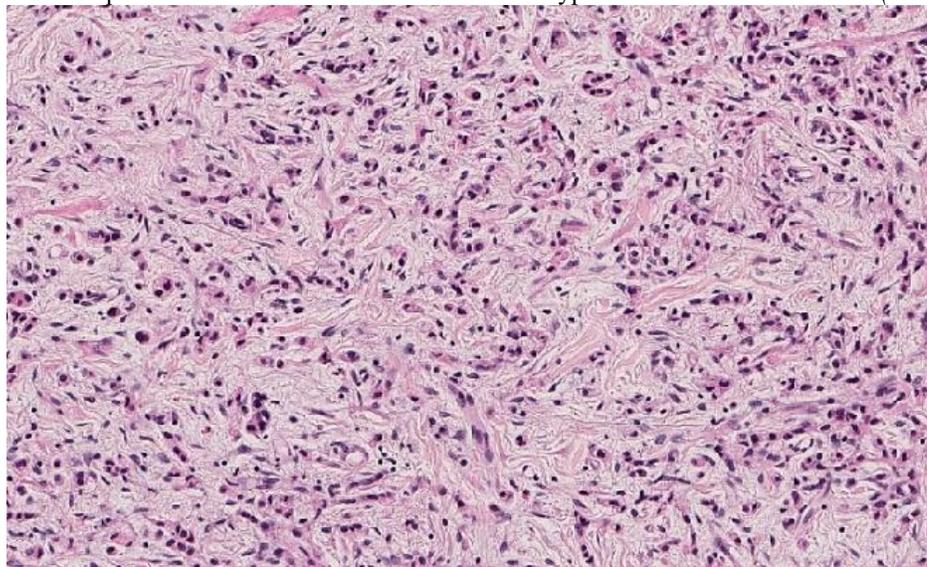

Figure 6: Diffuse type gastric adenocarcinoma (Neoplastic cells scattered and forming small rows with low cohesion, surrounded by an intense desmoplastic reaction). In this case, the neoplastic cells are small and show a variable amount of eosinophilic cytoplasm (with no signet ring cell morphology) corresponding to the poorly cohesive, NOS subtype of the WHO classification *(Martínez,2025)*

Diagnostic Role of Immunohistochemistry in Gastric Carcinoma

Immunohistochemistry (IHC) plays a pivotal role in the diagnostic evaluation of gastric carcinoma, particularly in cases where routine histomorphology is insufficient to establish tumor lineage, differentiation, or primary origin. In daily surgical pathology practice, gastric biopsies are often small, fragmented, and affected by inflammation, ulceration, or treatment-related changes, all of which may

obscure architectural features. Under these circumstances, IHC provides essential adjunctive information that enhances diagnostic accuracy and reproducibility [46,47].

One of the primary diagnostic applications of immunohistochemistry in gastric carcinoma is confirmation of epithelial origin. Poorly differentiated tumors, especially those composed of discohesive or solid sheets of atypical cells, may mimic lymphomas, neuroendocrine neoplasms, melanomas, or metastatic carcinomas from other sites. Broad-spectrum cytokeratin immunostains are routinely used to establish epithelial differentiation and exclude non-epithelial malignancies, particularly in small biopsies and metastatic settings [48,49]. This step is fundamental before further subtyping or biomarker evaluation is undertaken.

Immunohistochemistry is also valuable in supporting histological subtyping when morphologic features overlap or are ambiguous. For example, distinguishing intestinal-type gastric carcinoma from diffuse or poorly cohesive carcinoma may be challenging in limited tissue samples or in tumors with mixed growth patterns. In such cases, immunophenotypic evidence of glandular differentiation or loss of cell cohesion can complement histological assessment and increase diagnostic confidence [50,51]. This is particularly relevant because histological subtype carries important prognostic and therapeutic implications.

Another important diagnostic application of IHC in gastric carcinoma is the distinction between primary gastric tumors and metastatic malignancies involving the stomach. The stomach is a recognized site of metastasis for carcinomas originating from the breast, lung, pancreas, esophagus, and colorectum. Immunohistochemical profiling, interpreted in conjunction with clinical and radiologic information, assists in determining the site of origin in these challenging cases [52,53]. Accurate classification is critical, as misdiagnosis may lead to inappropriate staging and management.

Immunohistochemistry further aids in the identification and characterization of uncommon and rare histological variants of gastric carcinoma. Entities such as gastric carcinoma with lymphoid stroma, hepatoid adenocarcinoma, adenosquamous carcinoma, and fundic gland–type adenocarcinoma exhibit distinct immunophenotypic patterns that support their recognition and distinction from more common adenocarcinoma subtypes [54–56]. Correct identification of these variants is essential, as they differ substantially in prognosis, biological behavior, and therapeutic response.

In the evaluation of early gastric neoplasia and precursor lesions, immunohistochemistry may assist in differentiating high-grade dysplasia from intramucosal carcinoma, particularly in diagnostically challenging cases. Although the diagnosis remains primarily morphologic, altered expression of proliferation- and differentiation-related markers may provide supportive evidence when architectural and cytologic criteria are borderline [57,58]. Nevertheless, immunohistochemistry should be interpreted cautiously in this setting and should not replace established histopathological criteria.

Importantly, the diagnostic use of immunohistochemistry in gastric carcinoma must be guided by careful marker selection and awareness of normal gastric mucosal expression patterns. Background staining in non-neoplastic epithelium, metaplastic mucosa, and inflammatory cells can lead to diagnostic pitfalls if not properly contextualized [59]. Standardization of staining protocols and adherence to evidence-based diagnostic algorithms are therefore essential to ensure reliable and clinically meaningful results.

In summary, immunohistochemistry serves as a critical adjunct to morphology in the diagnostic workup of gastric carcinoma. It enhances tumor classification, resolves difficult differentials, and supports accurate identification of primary gastric malignancies and their variants. These diagnostic applications form the foundation upon which prognostic stratification and predictive biomarker assessment are built, as discussed in the following sections.

Immunohistochemistry for Prognostic Stratification in Gastric Carcinoma

Beyond its diagnostic utility, immunohistochemistry plays a crucial role in the prognostic stratification of gastric carcinoma. Gastric cancer exhibits marked variability in clinical behavior even within the same histological subtype and pathological stage, highlighting the limitations of morphology-based prognostication alone. Immunohistochemical evaluation allows assessment of tumor biological characteristics related to proliferation, differentiation, invasion, and interaction with the tumor

microenvironment, thereby providing additional prognostic information that complements conventional staging systems [60,61].

Tumor differentiation and growth pattern remain important prognostic indicators in gastric carcinoma, and immunohistochemistry may support their evaluation, particularly in poorly differentiated tumors. Loss of glandular differentiation and acquisition of poorly cohesive growth are associated with aggressive behavior, early dissemination, and unfavorable outcomes. Immunophenotypic alterations reflecting disrupted epithelial differentiation and increased cellular plasticity often parallel these morphologic changes and correlate with adverse prognosis [62,63]. Such findings reinforce the value of integrating immunohistochemical data with histological grading.

The assessment of tumor proliferation represents another important prognostic application of immunohistochemistry. Increased proliferative activity is generally associated with higher tumor grade, advanced stage, and reduced survival. Immunohistochemical markers of cell cycle activity provide a practical means of estimating tumor growth fraction and have been shown to correlate with disease progression and patient outcome in gastric carcinoma [64,65]. While not routinely included in standardized reporting, proliferation indices may offer supplementary prognostic insight in selected cases.

Angiogenesis and stromal remodeling are key components of tumor progression and metastasis in gastric carcinoma. Immunohistochemical evaluation of tumor-associated vasculature and stromal activation reflects the biological aggressiveness of the tumor and has been linked to lymphovascular invasion, nodal metastasis, and poor survival [66,67]. These features are particularly relevant in advanced-stage disease and underscore the importance of the tumor microenvironment in shaping clinical outcomes.

Increasing attention has been directed toward the prognostic significance of the immune microenvironment in gastric carcinoma. Immunohistochemical assessment of tumor-infiltrating immune cells provides insight into host antitumor responses and has demonstrated strong associations with prognosis. Tumors characterized by dense lymphoid infiltration, such as gastric carcinoma with lymphoid stroma, generally exhibit more favorable outcomes, whereas immune-desert or immune-excluded phenotypes are often associated with aggressive disease and resistance to therapy [68–70]. These observations highlight the prognostic relevance of immune contexture in gastric cancer pathology.

Microsatellite instability represents a distinct biological subtype of gastric carcinoma with important prognostic implications. MSI-high tumors are characterized by defective DNA mismatch repair and typically demonstrate increased immune cell infiltration and improved survival compared with microsatellite-stable tumors. Immunohistochemistry serves as a reliable surrogate for MSI status and enables identification of this prognostically favorable subgroup in routine practice [71–73]. Recognition of MSI status is therefore essential not only for prognostic assessment but also for therapeutic planning.

Epstein–Barr virus–associated gastric carcinoma constitutes another molecularly defined subgroup with unique prognostic features. These tumors often show prominent lymphoid stroma and distinct immunophenotypic profiles and are associated with improved survival relative to EBV-negative gastric carcinomas [74–76]. Immunohistochemical and in situ hybridization–based detection of EBV-related changes assists in identifying this subgroup and contributes to refined prognostic stratification.

Despite the growing body of evidence supporting immunohistochemical prognostic markers, several challenges remain. Tumor heterogeneity, variability in scoring methods, and lack of standardized cut-off values limit the routine implementation of many prognostic markers. Moreover, the prognostic significance of individual biomarkers may vary depending on tumor stage, histological subtype, and treatment context [77]. Consequently, prognostic immunohistochemistry should be interpreted within a comprehensive pathological and clinical framework.

In summary, immunohistochemistry provides valuable prognostic information in gastric carcinoma by reflecting tumor biology, host immune response, and molecular alterations. When integrated with histological classification and staging, immunohistochemical prognostic markers enhance risk stratification and support more individualized patient management. The prognostic insights gained through IHC also form the basis for predictive biomarker assessment, which is discussed in the following section.

Predictive Biomarkers and Immunohistochemistry-Guided Therapy in Gastric Carcinoma

Immunohistochemistry has become central to the identification of predictive biomarkers in gastric carcinoma, directly influencing therapeutic decision-making in the era of precision oncology. Unlike prognostic markers, which provide information about disease outcome irrespective of treatment, predictive biomarkers identify patients who are likely to benefit from specific targeted or immune-based therapies. In gastric carcinoma, several predictive biomarkers have been validated and incorporated into clinical guidelines, with immunohistochemistry serving as the primary screening and diagnostic modality in routine practice [78,79].

Human epidermal growth factor receptor 2 (HER2) overexpression represents one of the earliest and most clinically established predictive biomarkers in gastric carcinoma. HER2-positive gastric cancers constitute a distinct subgroup for which targeted anti-HER2 therapy has demonstrated survival benefit. Immunohistochemistry is the first-line method for HER2 assessment, allowing evaluation of protein overexpression and guiding selection of cases for confirmatory in situ hybridization testing when appropriate [80–82]. Accurate interpretation of HER2 staining in gastric carcinoma requires awareness of tumor heterogeneity, incomplete membranous staining patterns, and differences in scoring criteria compared with breast carcinoma [83].

Mismatch repair (MMR) deficiency and microsatellite instability represent another critical predictive biomarker axis in gastric carcinoma. Tumors with defective MMR proteins exhibit high mutational burden and increased neoantigen formation, rendering them particularly responsive to immune checkpoint inhibition. Immunohistochemical assessment of MMR protein expression provides a robust and cost-effective approach for identifying MSI-high gastric carcinomas and is increasingly recommended as part of routine diagnostic evaluation [84–86]. Recognition of MSI status carries both predictive and prognostic implications.

Programmed death-ligand 1 (PD-L1) expression has emerged as a key predictive biomarker for immunotherapy in gastric carcinoma. Immunohistochemical evaluation of PD-L1 expression, particularly using combined positive scoring systems that incorporate both tumor cells and immune cells, assists in identifying patients who may benefit from immune checkpoint inhibitors [87–89]. However, PD-L1 interpretation remains challenging due to intratumoral heterogeneity, inter-assay variability, and evolving scoring thresholds across clinical trials [90].

Epstein–Barr virus–associated gastric carcinoma represents a distinct molecular subgroup with important predictive implications. These tumors frequently demonstrate dense immune infiltration, elevated PD-L1 expression, and unique epigenetic and transcriptomic alterations that confer sensitivity to immune checkpoint blockade. Immunohistochemical and in situ hybridization–based identification of EBV-associated tumors therefore provides clinically actionable predictive information [91–93].

Emerging Biomarkers: Cadherin-11 and Tropomyosin-1

Beyond established predictive biomarkers, increasing attention has been directed toward molecules involved in cell adhesion, cytoskeletal organization, and epithelial–mesenchymal plasticity as potential therapeutic and biologic markers in gastric carcinoma. Cadherin-11 (CDH11), a type II classical cadherin, has been implicated in tumor invasion, stromal interaction, and metastatic behavior across multiple malignancies. Experimental and translational studies suggest that altered CDH11 expression may influence tumor cell motility, epithelial–mesenchymal transition, and response to cytotoxic agents, highlighting its potential relevance as an emerging biomarker in gastric cancer biology [94–97].

In gastric carcinoma specifically, aberrant CDH11 expression has been associated with tumor progression, invasive behavior, and chemoresistance in experimental models. Immunohistochemical evaluation of CDH11 provides insight into tumor–stromal interactions and mesenchymal-like phenotypes that may underlie aggressive clinical behavior [98–100]. Although CDH11 is not yet a validated predictive biomarker in clinical practice, its involvement in signaling pathways linked to therapeutic resistance suggests potential future relevance, particularly in the context of combination therapies targeting tumor–stroma crosstalk.

Tropomyosin-1 (TPM1), a cytoskeletal actin-binding protein, has also emerged as a molecule of interest in cancer research. TPM1 plays a critical role in maintaining cytoskeletal stability and regulating cell shape, motility, and adhesion. In multiple tumor types, loss or downregulation of TPM1 has been associated with enhanced proliferation, invasion, angiogenesis, and metastatic potential [101–104]. These biological functions position TPM1 as a candidate tumor suppressor whose altered expression may influence treatment response.

In gastric carcinoma and related gastrointestinal malignancies, TPM1 dysregulation has been linked to epithelial–mesenchymal transition and cytoskeletal remodeling, processes that are increasingly recognized as contributors to therapeutic resistance and disease progression. Immunohistochemical assessment of TPM1 expression may therefore provide indirect information regarding tumor plasticity and invasive potential, although its predictive value remains investigational [105–107].

At present, neither Cadherin-11 nor Tropomyosin-1 is incorporated into routine predictive biomarker panels for gastric carcinoma. Nevertheless, their emerging roles in tumor biology underscore the expanding scope of immunohistochemistry beyond established targets. As molecularly guided therapies evolve, immunohistochemical evaluation of such markers may contribute to refined biological stratification and the development of novel therapeutic strategies.

In summary, immunohistochemistry remains indispensable for predictive biomarker assessment in gastric carcinoma, enabling identification of patients eligible for targeted and immune-based therapies. While established markers such as HER2, MMR/MSI, PD-L1, and EBV status currently guide clinical management, emerging biomarkers including Cadherin-11 and Tropomyosin-1 highlight future directions for biologically informed therapy and reinforce the central role of pathology in precision oncology.

References

1. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. *Int J Mol Sci*. 2020;21(11):4012. doi:10.3390/ijms21114012

2. Lin Y, Zheng Y, Wang HL, Wu J. Global patterns and trends in gastric cancer incidence rates (1988–2012) and predictions to 2030. *Gastroenterology*. 2021;161(1):116-127. doi:10.1053/j.gastro.2021.03.018

3. Resende C, Thiel A, Machado JC, Ristimäki A. Gastric cancer: basic aspects. *Helicobacter*. 2011;16(Suppl 1):38-44. doi:10.1111/j.1523-5378.2011.00880.x

4. Kim TH, Kim IH, Kang SJ, et al. Korean practice guidelines for gastric cancer 2022: an evidence-based, multidisciplinary approach. *J Gastric Cancer*. 2023;23(1):3. doi:10.5230/jgc.2023.23.e3

5. Yuan S, Li L, Xiang S, Jia H, Luo T. Cadherin-11 is inactivated due to promoter methylation and functions as a tumor suppressor in colorectal cancer. *Cancer Manag Res*. 2019;11:2517-2529. doi:10.2147/CMAR.S193921

6. Chen PF, Wang F, Nie JY, et al. Co-expression network analysis identified CDH11 in association with progression and prognosis in gastric cancer. *Onco Targets Ther*. 2018;11:6425-6436. doi:10.2147/OTT.S173346

7. Tian Z, Zhao J, Wang Y. The prognostic value of TPM1–4 in hepatocellular carcinoma. *Cancer Med*. 2022;11(2):433-446. doi:10.1002/cam4.4478

8. Wang J, Tang C, Yang C, Zheng Q, Hou Y. Tropomyosin-1 functions as a tumor suppressor with respect to cell proliferation, angiogenesis and metastasis in renal cell carcinoma. *J Cancer*. 2019;10(10):2220-2228. doi:10.7150/jca.28261

9. Pan H, Gu L, Liu B, et al. Tropomyosin-1 acts as a potential tumor suppressor in human oral squamous cell carcinoma. *PLoS One*. 2017;12(2):e0168900. doi:10.1371/journal.pone.0168900

10. McQuilken SA. The mouth, stomach and intestines. *Anaesth Intensive Care Med*. 2021;22(5):330-335.

11. Ban S. The normal stomach: anatomy, histology, and specimen dissection relevant to pathological practice. In: *Morson and Dawson's Gastrointestinal Pathology*. 6th ed. Elsevier; 2024:109-127.

12. Hsu M, Safadi AO, Lui F. Physiology, stomach. *StatPearls*. StatPearls Publishing; 2023.

13. Hoffmann W. Self-renewal of the gastric epithelium from stem and progenitor cells. *Front Biosci (Schol Ed)*. 2013;5:720-731. doi:10.2741/s402

14. Chandan VS. Normal histology of gastrointestinal tract. In: *Surgical Pathology of Non-Neoplastic Gastrointestinal Diseases*. Springer; 2019:3-18.

15. Chaudhry SR, Liman MNP, Omole AE. Anatomy, abdomen and pelvis: stomach. *StatPearls*. StatPearls Publishing; 2024.

16. Yang H, Yang WJ, Hu B. Gastric epithelial histology and precancerous conditions. *World J Gastrointest Oncol*. 2022;14(2):396-410. doi:10.4251/wjgo.v14.i2.396

17. Xiao S, Zhou L. Gastric stem cells: physiological and pathological perspectives. *Front Cell Dev Biol*. 2020;8:571536. doi:10.3389/fcell.2020.571536

18. Ercan F, Akakın D, Cilingir-Kaya OT. Histological features of the esophagus, stomach, and colon. In: *Risk Factors and Therapy of Esophagus Cancer*. Springer; 2024:101-114.

19. Arai J, Hayakawa Y, Tateno H, et al. The role of gastric mucins and mucin-related glycans in gastric cancers. *Cancer Sci*. 2024;115(9):2853-2861. doi:10.1111/cas.16282

20. Morgan E, Arnold M, Camargo MC, et al. The current and future incidence and mortality of gastric cancer. *EClinicalMedicine*. 2022;47:101404. doi:10.1016/j.eclinm.2022.101404

21. Song MJ, Park YS, Song HJ, et al. Prognosis of pregnancy-associated gastric cancer. *Gut Liver*. 2016;10(5):731-738. doi:10.5009/gnl15323

22. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones and gastric cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2012;21(1):20-38. doi:10.1158/1055-9965.EPI-11-0834

23. Lin JL, Lin JX, Lin GT, et al. Global incidence and mortality trends of gastric cancer. *BMC Public Health*. 2024;24:1763.

24. Gonzalez RS, Farris AB. Overview of current concepts in gastric intestinal metaplasia and gastric cancer. *Gastroenterol Hepatol*. 2018;14(2):92-101.

25. Min BH. Early diagnosis and risk assessment of gastric cancer. *Korean J Helicobacter Upper Gastrointest Res*. 2024;24(4):307.

26. El Mazny AN, Hishmat T, Hussein A, Gaith D. Prevalence of Helicobacter pylori cagA among patients with gastric cancer. *Egypt J Intern Med*. 2019;31(4):522-528.

27. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, Polkowski WP. Gastric cancer: epidemiology, prevention, classification, and treatment. *Cancer Manag Res*. 2018;10:239-248.

28. Kulig P, Nowakowski P, Sierzęga M, et al. Prognostic factors in gastric cancer resection. *Anticancer Res*. 2021;41(7):3523-3534. doi:10.21873/anticanres.15135

29. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev*. 2014;23(5):700-713. doi:10.1158/1055-9965.EPI-13-1057

30. McLean MH, El-Omar EM. Genetics of gastric cancer. *Nat Rev Gastroenterol Hepatol*. 2014;11:664-674. doi:10.1038/nrgastro.2014.143

31. Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. E-cadherin alterations in hereditary diffuse gastric cancer. *Prog Mol Biol Transl Sci*. 2013;116:337-359.

32. Worthley DL, Phillips KD, Wayte N, et al. Gastric adenocarcinoma and proximal polyposis of the stomach. *Gut*. 2012;61(5):774-779. doi:10.1136/gutjnl-2011-300348

33. Gullo I, Grillo F, Mastracci L, et al. Precancerous lesions of the stomach and hereditary gastric cancer syndromes. *Pathologica*. 2020;112(3):166.

34. Gullo I, van der Post RS, Carneiro F. Recent advances in pathology of heritable gastric cancer syndromes. *Histopathology*. 2021;78(1):125-147. doi:10.1111/his.14228

35. Masciari S, Dewanwala A, Stoffel E, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. *Genet Med*. 2011;13:651-657.

36. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. Cancer risk in Peutz-Jeghers syndrome. *Am J Gastroenterol*. 2010;105(6):1258-1265. doi:10.1038/ajg.2009.725

37. Garrean S, Hering J, Saied A, et al. Gastric adenocarcinoma arising from fundic gland polyps in FAP. *Am Surg*. 2008;74(1):79-83.

38. Mamun TI, Younus S, Rahman MH. Gastric cancer: epidemiology and risk factors. *Cancer Treat Res Commun*. 2024;41:100845. doi:10.1016/j.ctarc.2024.100845

39. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020. *Int J Cancer*. 2021;149(4):778-789. doi:10.1002/ijc.33588

40. Li WY, Han Y, Xu HM, et al. Smoking and gastric cancer risk. *BMC Cancer*. 2019;19(1):377.

41. Li Y, Eshak ES, Shirai K, et al. Alcohol consumption and gastric cancer risk. *J Epidemiol*. 2021;31(1):30-36.

42. Ko KP. Risk factors of gastric cancer and lifestyle modification. *J Gastric Cancer*. 2024;24(1):99-107.

43. Choi IJ, Kim CG, Lee JY, et al. Family history and Helicobacter pylori treatment. *N Engl J Med*. 2020;382(5):427-436.

44. Jung YS, Tran MTX, Park B, Moon CM. Family history and gastric cancer risk. *Am J Gastroenterol*. 2022;117(8):1255-1263.

45. Cuzzuol BR, Vieira ES, Araújo GRL, et al. Gastric cancer: a brief review. *Arch Gastroenterol Res*. 2020;1(2):34-39.

46. Salvatori S, Marafini I, Laudisi F, Monteleone G, Stolfi C. Helicobacter pylori and gastric cancer. *Int J Mol Sci*. 2023;24(3):2895.

47. den Hollander WJ, Holster IL, den Hoed CM, et al. Surveillance of premalignant gastric lesions. *Gut*. 2019;68(4):585-593.

48. Gupta S, Li D, El-Serag HB, et al. AGA guidelines on gastric intestinal metaplasia. *Gastroenterology*. 2020;158(3):693-702.

49. Sun K, Jia K, Lv H, et al. EBV-positive gastric cancer. *Front Oncol*. 2020;10:583463.

50. Tavakoli A, Monavari SH, Solaymani Mohammadi F, et al. EBV and gastric cancer. *BMC Cancer*. 2020;20(1):493.

51. Saito M, Kono K. Landscape of EBV-positive gastric cancer. *Gastric Cancer*. 2021;24(5):983-989.

52. Matsusaka K, Kaneda A, Nagae G, et al. Classification of EBV-positive gastric cancers. *Cancer Res*. 2011;71(23):7187-7197.

53. Liang Q, Yao X, Tang S, et al. EBV-associated mutations in gastric cancer. *Gastroenterology*. 2014;147(6):1350-1362.

54. Tanabe H, Mizukami Y, Takei H, et al. EBV and MSI subtypes of early gastric neoplasms. *J Pathol Clin Res*. 2021;7(4):397-409.

55. Rodriquenz MG, Roviello G, D'Angelo A, et al. MSI and EBV-positive gastric cancers. *J Clin Med*. 2020;9(5):1427.

56. Møller P, Seppälä T, Bernstein I, et al. Lynch syndrome cancer incidence. *Gut*. 2017;66(9):1657-1664.

57. Shen S, Chen X, Li H, Sun L, Yuan Y. MLH1 promoter methylation in gastric cancer. *J Cancer*. 2018;9(11):1932-1942.

58. Miceli R, An J, Di Bartolomeo M, et al. Prognostic impact of MSI in gastric cancer. *Oncology*. 2019;97(1):38-43.

59. Cai H, Jing C, Chang X, et al. Mutational landscape of gastric cancer. *J Transl Med*. 2019;17(1):189.

60. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202-209.

61. Cristescu R, Lee J, Nebozhyn M, et al. Molecular subtypes of gastric cancer. *Nat Med*. 2015;21(5):449-456.

62. Zheng X, Wang J, Wei L, et al. EBV microRNA inhibits p53. *J Virol*. 2018;92(23):e01677-16.

63. Yao X, Ajani JA, Song S. Molecular biology of gastric cancer peritoneal metastasis. *Transl Gastroenterol Hepatol*. 2020;5:57.

64. Huang L, Wu RL, Xu AM. Epithelial–mesenchymal transition in gastric cancer. *Am J Transl Res*. 2015;7(11):2141-2158.

65. Gan L, Xu M, Hua R, et al. EZH2 induces EMT in gastric cancer. *J Hematol Oncol*. 2018;11:9.

66. Liu J, Wang G, Zhao J, et al. LncRNA H19 and EMT in gastric cancer. *Dig Dis*. 2022;40(4):436-447.

67. Matsuoka T, Yashiro M. Tumor microenvironment in gastric cancer. *Int J Mol Sci*. 2024;25(21):11735.

68. Pernot S, Terme M, Radosevic-Robin N, et al. Immune infiltrates and Lauren classification. *Gastric Cancer*. 2020;23(1):73-81.

69. Kim M, Seo AN. Molecular pathology of gastric cancer. *J Gastric Cancer*. 2022;22(4):273-290.

70. Nshizirungu JP, Bennis S, Mellouki I, et al. TCGA and ACRG classification validation. *Dis Markers*. 2021;2021:9980410.

71. Röcken C. Predictive biomarkers in gastric cancer. *J Cancer Res Clin Oncol*. 2023;149(1):467-481.

72. Maleki SS, Röcken C. Chromosomal instability in gastric cancer. *Neoplasia*. 2017;19(5):412-420.

73. Tsai CK, Yeh TS, Wu RC, et al. Metabolomic alterations and CIN. *World J Gastroenterol*. 2018;24(33):3760-3769.

74. Wang Q, Liu G, Hu C. Molecular classification of gastric adenocarcinoma. *Gastroenterol Res*. 2019;12(6):275-282.

75. Zhang R, Liu Z, Chang X, et al. Chromosomal integrity in gastric cancers. *Int J Biol Markers*. 2022;37(3):296-305.

76. Nemtsova MV, Kuznetsova EB, Bure IV. Chromosomal instability in gastric cancer. *Int J Mol Sci*. 2023;24(23):16961.

77. Oue N, Sentani K, Sakamoto N, et al. Molecular carcinogenesis and mucin phenotype. *Int J Clin Oncol*. 2019;24:771-778.

78. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.

79. Wang Q, Wang L, Li Y, Zhang Y. Prognostic significance of histological grade. *BMC Cancer*. 2021;21:1065.

80. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018. *CA Cancer J Clin*. 2018;68(6):394-424.

81. Zhao B, Mei D, Lv W, et al. Prognostic factors in young gastric cancer patients. *J Adolesc Young Adult Oncol*. 2020;9(4):514-521.

82. Alshehri A, Alanezi H, Kim BS. Prognostic factors by sex and age. *World J Clin Cases*. 2020;8(9):1608-1618.

83. Choi Y, Kim N, Kim KW, et al. Sex-based differences in gastric cancer. *World J Gastroenterol*. 2022;28(9):933-944.

84. Lopez MJ, Carbajal J, Alfaro AL, et al. Global characteristics of gastric cancer. *Crit Rev Oncol Hematol*. 2023;181:103841.

85. Ashktorab H, Kupfer SS, Brim H, Carethers JM. Racial disparities in GI cancer. *Gastroenterology*. 2017;153(4):910-923.

86. Kumar S, Metz DC, Ellenberg S, et al. Risk of gastric cancer after H. pylori infection. *Gastroenterology*. 2020;158(3):527-536.

87. Petrelli F, Ghidini M, Barni S, et al. Prognostic role of tumor location. *Ann Surg Oncol*. 2017;24(9):2655-2668.

88. Fujikawa K, Omori T, Shinno N, et al. Tumor deposits and recurrence. *J Gastrointest Surg*. 2023;27(7):1336-1344.

89. Riihimäki M, Hemminki A, Sundquist K, et al. Metastatic spread in gastric cancer. *Oncotarget*. 2016;7(32):52307-52316.

90. Yang WJ, Zhao HP, Yu Y, et al. Global epidemiology and prognostic factors. *World J Gastroenterol*. 2023;29(16):2452-2468.

91. Shah SC, Piazuelo MB, Kuipers EJ, Li D. Histologic subtyping of gastric intestinal metaplasia. *Gastroenterology*. 2020;158(3):705-731.

92. Huang RJ, Choi AY, Truong CD, et al. Diagnosis and management of gastric intestinal metaplasia. *Gut Liver*. 2019;13(6):596-606.

93. Du S, Yang Y, Fang S, et al. Gastric cancer risk of intestinal metaplasia subtypes. *Clin Transl Gastroenterol*. 2021;12(10):e00402.

94. Laszkowska M, Truong H, Faye A, et al. Progression of gastric intestinal metaplasia. *Gastrointest Endosc*. 2022;96(4):765-773.

95. Gullo I, Grillo F, Mastracci L, et al. Precancerous gastric lesions. *Pathologica*. 2020;112(3):166.

96. White DL, Thompson SA, Lee JK. Gastric dysplasia progression. *Gastroenterology*. 2022;162(4):1234-1242.

97. Nagtegaal ID, Odze RD, Klimstra D, et al. WHO classification of digestive system tumours. *Histopathology*. 2020;76(2):182-188.

98. Arteaga C, Wadhwa R. Gastric polyp. *StatPearls*. StatPearls Publishing; 2024.

99. Waldum H, Fossmark R. Gastritis, gastric polyps and gastric cancer. *Int J Mol Sci*. 2021;22(12):6548.

100. Markowski AR, Markowska A, Guzinska-Ustymowicz K. Gastric hyperplastic polyps. *World J Gastroenterol*. 2016;22(40):8883-8891.

101. Islam RS, Patel NC, Lam-Himlin D, Nguyen CC. Gastric polyps. *Gastroenterol Hepatol*. 2013;9(10):640-651.

102. Castro R, Pimentel-Nunes P, Dinis-Ribeiro M. Gastric epithelial polyps. *Best Pract Res Clin Gastroenterol*. 2017;31(4):381-387.

103. Costa D, Ramai D, Tringali A. Novel classification of gastric polyps. *World J Gastroenterol*. 2024;30(31):3640-3653.

104. Olmez S, Sayar S, Saritas B, et al. Evaluation of gastric polyps. *North Clin Istanb*. 2018;5(1):41-46.

105. Kanai H, Kasuga K, Katakai S, et al. Gastric adenocarcinoma arising in fundic gland polyp. *Clin J Gastroenterol*. 2025;18(5):793-798.

106. Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to Helicobacter pylori. *Int J Cancer*. 2015;136(2):487-490.

107. Kotilea K, Bontems P, Touati E. Epidemiology and risk factors of Helicobacter pylori infection. *Adv Exp Med Biol*. 2019;1149:17-33. doi:10.1007/5584_2019_357