Article Type: Review Article
Volume 2, Issue 2

INTERNATIONAL JOURNAL OF CLINICAL & MEDICAL CASE STUDIES

Risk and screening of stomach cancer in patients with Biermer's disease: A clinical and scientific review

Abstract

Biermer's disease, or pernicious anemia, is an autoimmune atrophic gastritis characterized by the destruction of gastric parietal cells, a deficiency in intrinsic factor, and a lack of vitamin B12. Although widely recognized for its hematological and neurological effects, this disease also constitutes a high-risk environment for the development of neoplasms, particularly in the stomach. This review explores the links between Biermer's disease and gastric cancer, integrating the latest epidemiological, pathophysiological, histological, and clinical data. The review highlights the immune mechanisms underlying carcinogenesis, particularly the role of chronic inflammation, intestinal metaplasia, and dysplasia, which increase the risk of malignant transformation of gastric cells. We also discuss the various types of gastric cancers associated with this condition, including adenocarcinomas and type I gastric carcinoids, as well as the recommended endoscopic surveillance strategies. Current data suggest that regular endoscopic examinations and thorough histological evaluation of gastric lesions are essential for early detection and optimal treatment. Additionally, this review examines research avenues aimed at improving the prevention and management of these cancers, focusing on recent advances in biomarker identification and personalized treatments.

Keywords: Biermer's disease; Pernicious anemia; Atrophic gastritis; Gastric cancer; Carcinogenesis; Endoscopic surveillance.

Emmanuel Andrès[1]*; Jean Edouard Terrade[1]; Maria Belén Alonso Ortiz[2]; Xavier Jannot[1]; Manuel Méndez Bailón[3]; Gérard Gay[4]; Thierry Lavigne[5]; N Lorenzo-Villalba[1]

[1]Department of Internal Medicine, Hautepierre Hospital, University Hospitals of Strasbourg, Strasbourg, France.
[2]Department of Internal Medicine, University Hospital of Gran Canaria Dr. Negrín, Spain.
[3]Department of Internal Medicine, Hospital Universitario Clínico San Carlos, Spain.
[4]Department of Hepatology and Gastroenterology, New Civil Hospital, University Hospitals of Strasbourg, Strasbourg, France.
[5]Department of Hospital Hygiene and Public Health, Civil Hospital, University Hospitals of Strasbourg, Strasbourg, France.

***Corresponding author:** **Emmanuel Andrès**
Department of Internal Medicine, Hautepierre Hospital, University Hospitals of Strasbourg, Strasbourg, France.
Email: emmanuel.andres@chru-strasbourg.fr

Received: Nov 04, 2025
Accepted: Dec 02, 2025
Published Online: Dec 09, 2025
Journal: International Journal of Clinical & Medical Case Studies

Copyright: © **Andrès E** (2025). *This Article is distributed under the terms of Creative Commons Attribution 4.0 International License*

Introduction

Pernicious Anemia (PA), first described by Anton Biermer in 1872, is a chronic autoimmune disorder characterized by vitamin B12 (cobalamin) deficiency secondary to fundic atrophic gastritis. The condition results from a progressive immune-mediated destruction of gastric parietal cells, leading to the loss of intrinsic factor secretion, which is essential for intestinal B12 absorption. Classified among macrocytic anemias, PA typically presents with hematological manifestations (megaloblastic anemia) and neurological symptoms due to central and peripheral demyelination, which may occasionally occur even in the absence of anemia. Beyond these well-documented manifestations, a clinically significant yet less emphasized aspect of PA is its oncogenic potential. Indeed, autoimmune chronic atrophic gastritis is recognized by the *World Health Organization* (WHO) as a precancerous condition because of its strong association with the development of gastric adenocarcinoma

and type 1 neuroendocrine tumors. Several studies have confirmed that patients with PA have a 2- to 6-fold increased risk of developing gastric cancer compared with the general population (Vannella et al. 2010) [34]. Correa's cascade, which describes the progression from chronic inflammation to atrophy, intestinal metaplasia, dysplasia, and ultimately carcinoma, also applies to PA. The atrophic gastric microenvironment—characterized by pro-inflammatory cytokines such as Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α)—together with alterations in the gastric microbiota (particularly under prolonged hypochlorhydria), promotes this malignant transformation.

In this context, the present review aims to provide an in-depth analysis of the pathophysiological, epidemiological, and clinical mechanisms linking PA to an increased risk of gastric cancer, in light of the most recent evidence from the literature. Particular attention will be devoted to current strategies for screening, endoscopic surveillance, and management in this high-risk population.

Pathophysiology of pernicious anemia and its neoplastic predisposition

Gastric autoimmunity and parietal cell destruction

PA, Biermer's disease, is classified among organ-specific autoimmune diseases in which the immune system, through an aberrant response, targets and destroys specific components of the body. In PA, the autoimmune aggression is primarily directed against the gastric parietal cells, which play a key role in the secretion of hydrochloric acid and intrinsic factor. Intrinsic factor is essential for the intestinal absorption of B12, and its deficiency leads to metabolic disturbances associated with B12 depletion, notably macrocytic anemia and neurological disorders. The main autoantibodies identified in PA are directed against two major targets: the gastric parietal cells (anti-parietal cell antibodies) and intrinsic factor (anti–intrinsic factor antibodies). These autoantibodies are widely used as diagnostic markers in clinical practice, although their presence is not exclusive to this disease, and their absence does not necessarily exclude the diagnosis of PA [1]. Progressive destruction of the parietal cells leads to hypochlorhydria and, ultimately, achlorhydria, resulting in an altered gastric environment with a markedly reduced capacity to produce gastric acid. This phenomenon is associated with several key pathophysiological consequences:

- **Disruption of the mucosal barrier:** Hypochlorhydria compromises the integrity of the gastric mucosal barrier, rendering it more susceptible to exogenous insults such as bacterial infections and the penetration of carcinogenic agents.
- **Bacterial overgrowth:** The lack of hydrochloric acid permits the proliferation of bacteria that are normally inhibited by gastric acidity, increasing the risk of infections, particularly with *Helicobacter pylori*, which plays a central role in chronic gastritis and gastric carcinogenesis [2].
- **Formation of carcinogenic nitrites:** Hypochlorhydria favors the conversion of dietary nitrates into nitrites—well-established carcinogenic compounds—which promote the formation of N-nitroso derivatives, potent DNA-mutating agents and key drivers of gastric carcinogenesis [3].

Thus, gastric autoimmunity in PA extends far beyond a mere B12 deficiency; it creates a biologically permissive environment for multiple pathological processes, including those leading to severe gastric diseases such as gastric cancer.

Table 1: Causes and contributing factors for gastric cancer development in patients with pernicious anemia.

Cause / Contributing factor	Description	Mechanism
Atrophic gastritis	Progressive destruction of gastric parietal cells, leading to reduced gastric acid production	Hypochlorhydria promotes bacterial overgrowth and alters the gastric mucosa composition, contributing to chronic inflammation
Intestinal metaplasia	Transformation of gastric cells into cells resembling intestinal epithelium	Intestinal metaplasia is a major precursor to dysplasia and gastric adenocarcinoma
Gastric dysplasia	Cellular abnormalities in the gastric mucosa, often seen in advanced atrophic gastritis	Dysplasia indicates abnormal cellular transformation, increasing the risk of gastric cancer
Chronic inflammation	Persistent activation of the immune system in the stomach, resulting in chronic inflammation	Prolonged inflammation damages cellular DNA, promoting oncogenic mutations
Vitamin B12 and folate deficiency	Impaired absorption of vitamin B12 and other essential nutrients in the context of pernicious anemia	These deficiencies can impair DNA repair mechanisms and increase the risk of oncogenic mutations
Hypergastrinemia	Gastric acid deficiency can lead to increased gastrin production	Chronic hypergastrinemia stimulates gastric epithelial cell growth, promoting tumor development
Bacterial infections (Helicobacter pylori)	Chronic H. pylori infection, often associated with atrophic gastritis	H. pylori induces chronic inflammation and increases cytokine and enzyme production that damage DNA
Genetic factors	Genetic predisposition to gastric cancer in certain pernicious anemia subtypes	Genetic mutations or chromosomal abnormalities increase susceptibility to gastric cancer in families with history of disease
Environmental factors	High-salt diet, nitrates, processed meats, and smoking	These factors increase gastric cancer risk by damaging the gastric mucosa and promoting carcinogenic exposure
Family history of gastric cancer	Hereditary or family history of gastric cancers, especially in autoimmune contexts	Genetic and familial predispositions increase the risk of gastric oncogenesis

Intestinal metaplasia and the correa sequence

The development of gastric cancer is widely regarded as a multistep process that culminates in the transformation of normal gastric mucosa into malignant epithelium. This transformation is described by the Correa sequence, a classical model of gastric carcinogenesis encompassing five successive stages: chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia, and ultimately adenocarcinoma [22]. In the context of PA, this sequence is particularly relevant, as chronic gastric inflammation and parietal cell atrophy create a microenvironment conducive to intestinal metaplasia. Intestinal metaplasia represents

an adaptive response of the gastric mucosa in which native gastric epithelial cells transform into intestinal-type cells—a well-documented precancerous stage in gastric carcinogenesis. This transformation is driven by persistent inflammatory stimuli, notably pro-inflammatory cytokines such as Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α), which promote abnormal cell proliferation and impair DNA repair mechanisms [5]. Dysplasia represents the intermediate stage between metaplasia and invasive carcinoma and is characterized by histopathological alterations in gastric mucosal cells, including architectural distortion and nuclear atypia. At this point, the accumulation of genetic mutations within metaplastic cells enhances their oncogenic potential, ultimately leading to the formation of gastric adenocarcinoma [6]. It is well established that PA, through its autoimmune and inflammatory gastric atrophy, follows the Correa sequence, rendering it a high-risk condition for the development of gastric cancer. Moreover, recent studies have demonstrated that the prevalence of intestinal metaplasia and dysplasia is significantly higher among patients with PA than in the general population [7]. Thus, PA, through its chronic autoimmune and inflammatory processes, provides a fertile ground for the progression toward precancerous lesions, justifying careful surveillance to prevent the evolution toward gastric cancer.

Vitamin B12 deficiency and genetic instability

Vitamin B12 deficiency is a well-documented phenomenon observed in various pathological conditions, particularly in PA and other disorders associated with intrinsic factor deficiency or impaired B12 absorption. This deficiency plays a crucial role in cellular metabolism, DNA synthesis, and genetic stability. The long-term consequences of B12 deficiency, particularly its impact on genomic instability, can be profound and contribute to carcinogenesis—especially in gastric cancer, where cobalamin deficiency exerts a mutagenic effect [8]. The genetic instability associated with B12 deficiency arises from alterations in DNA replication and repair processes, increasing the risk of mutations and chromosomal abnormalities that may drive malignant transformation.

Effects of vitamin B12 deficiency on genetic instability

Vitamin B12 plays an essential role in DNA methylation, a key regulatory process for gene expression and the maintenance of genomic integrity. B12 deficiency disrupts methylation pathways, leading to global hypomethylation and genetic instability. This instability enhances the likelihood of mutations and DNA damage, which are critical mechanisms in carcinogenesis, including gastric cancer [9]. Genetic mutations induced by this instability often affect crucial genes involved in DNA repair and tumor suppression, thereby allowing neoplastic cells to proliferate unchecked.

Role of homocysteine in gastric cancer risk

A deficiency in vitamin B12 leads to elevated plasma homocysteine levels, an amino acid whose metabolism is tightly regulated by cobalamin. Increased homocysteine levels have been associated with chronic inflammation, oxidative stress, and DNA damage [10]. Homocysteine can also induce direct cytotoxic effects on gastric mucosal cells, creating a pro-mutagenic and pro-proliferative environment conducive to carcinogenesis. Thus, both B12 deficiency and the consequent rise in homocysteine levels contribute to an increased risk of gastric cancer through mechanisms involving inflammation, oxidative stress, and impaired DNA integrity.

***Helicobacter pylori* and pernicious anemia: antagonism or cofactor?**

Helicobacter pylori is a well-established gastric pathogen and the principal etiological agent of several gastric disorders, ranging from acute gastritis to chronic atrophic gastritis, and plays a central role in gastric cancer development through the Correa sequence. *H. pylori* induce a chronic local inflammatory response that, over time, can lead to mucosal destruction and progression toward more severe gastric pathologies such as gastric adenocarcinoma and Mucosa-Associated Lymphoid Tissue (MALT) lymphoma [12]. However, in PA, the situation differs markedly. This condition is an autoimmune gastritis primarily affecting the gastric fundus, where the autoimmune attack specifically targets the parietal cells responsible for secreting hydrochloric acid and intrinsic factor. This autoimmune process results in hypochlorhydria and the production of autoantibodies against both parietal cells and intrinsic factor. Paradoxically, *H. pylori* infection is often absent or only weakly detected in these patients (Sonnenberg et al. 1991). Several hypotheses have been proposed to explain this apparent lack of coinfection. One prominent theory suggests a competitive exclusion mechanism between the anti-parietal immune response and *H. pylori* infection, implying that activation of humoral and cellular immunity against gastric parietal cells may interfere with bacterial colonization [13]. In other words, the strong autoimmune inflammatory response directed against the gastric mucosa in PA may hinder *H. pylori* persistence. Nonetheless, coexistence of *H. pylori* infection and PA has been documented. In such cases, *H. pylori* may act as a synergistic factor, accelerating gastric atrophy and promoting chronic inflammation, which together enhance the risk of gastric carcinogenesis. Persistent *H. pylori*–induced inflammation, when superimposed on autoimmune atrophic gastritis, may therefore contribute to a microenvironment that fosters neoplastic transformation [14]. In clinical practice, the issue of detecting and eradicating *H. pylori* infection in patients with PA remains controversial. Some experts advocate systematic screening for *H. pylori*, particularly in patients with dyspeptic symptoms or evidence of gastric atrophy. If infection is confirmed, eradication therapy could theoretically slow the progression of atrophic changes and reduce malignant potential, although the actual benefits in this specific context remain debated [15].

Common variable immunodeficiency, aire, and complex autoimmune susceptibility

Common Variable Immunodeficiency (CVID) is a rare but serious disorder characterized by a multifaceted immune deficiency, in which patients exhibit increased susceptibility to infections, autoimmune diseases, and malignancies. Among the gastrointestinal manifestations associated with CVID, chronic lymphocytic gastritis is frequently observed. These gastritides may be autoimmune in nature and can mimic or overlap with PA in certain cases. Lymphocytic gastritis associated with CVID may also progress to complications such as gastric lymphoma, underscoring an increased risk of gastric cancer in this population [16]. Patients with CVID are at heightened risk for developing gastric and other solid tumors, warranting close clinical surveillance. CVID is often associated with profound abnormalities in adaptive immune regulation, which are partly modulated by proteins such as the *Autoimmune Regulator* (AIRE)—a key gene involved in central immune tolerance. The AIRE gene, expressed primarily in the thymus, plays an essential role in the deletion of autoreactive lymphocytes during thymic selection. Muta-

tions in this gene, which cause autoimmune polyendocrine syndrome type 1, lead to a breakdown of central immune tolerance, promoting the development of multiple autoimmune diseases. Certain AIRE gene variants have been associated with PA, suggesting that this condition may represent a gastrointestinal manifestation of a broader syndrome of defective immune tolerance [17]. This context of impaired immune tolerance—further amplified by genetic and environmental factors—may also contribute to susceptibility to gastric carcinogenesis. Mutations or dysfunction of AIRE could promote aberrant autoimmune reactions within the gastric mucosa, fostering a microenvironment characterized by chronic inflammation, intestinal metaplasia, and dysplasia—the precancerous steps leading to gastric adenocarcinoma [18]. Thus, PA may be conceptualized as the digestive component of a broader autoimmune syndrome in which defective central immune tolerance, interacting with local inflammatory intensity and genetic predisposition, constitutes a major determinant of neoplastic progression. This hypothesis highlights the need for further research into the underlying mechanisms and preventive strategies for gastric cancer in these patients.

Epidemiology of gastric cancer in pernicious anemia

Increased relative risk

Epidemiological studies and meta-analyses have consistently demonstrated that patients with PA exhibit an increased risk of developing gastric cancer, including both gastric adenocarcinoma and neuroendocrine (carcinoid) tumors. Multiple cohort studies have reported a significantly elevated Relative Risk (RR) of gastric cancer in this population, ranging from approximately 2.9 to 7.2 compared to the general population [19,20]. A comprehensive meta-analysis by Vannella et al. [21] further quantified this association, reporting a RR of 6.8 for gastric adenocarcinoma among patients with PA. Although the incidence of gastric neuroendocrine tumors is comparatively lower, it remains significantly elevated, with a RR of 2.3. These findings indicate that the chronic atrophic gastritis and disrupted immune tolerance characteristic of PA create a microenvironment favorable to neoplastic transformation [11]. Additional studies have corroborated this relationship, particularly in individuals with coexisting risk factors such as long-standing hypochlorhydria or intestinal metaplasia. The Correa sequence, a well-established model for gastric carcinogenesis, is highly relevant in PA, where atrophic gastritis and intestinal metaplasia represent key early stages in the multistep progression toward gastric cancer [4,23]. These observations emphasize the need for vigilant clinical surveillance in patients with PA to facilitate early detection of gastric neoplasia.

Time to cancer onset

Gastric cancer associated with PA typically develops after a prolonged course rather than at disease onset. On average, the latency period between the diagnosis of PA and the emergence of gastric neoplasia ranges from 10 to 15 years, although in some cases, gastric cancer may present concomitantly with the initial diagnosis of the autoimmune disorder [24,25]. This delay reflects the slow histopathological progression of chronic atrophic gastritis toward more advanced precancerous stages such as intestinal metaplasia and dysplasia. The transformation of normal gastric mucosa into malignant tissue occurs gradually over time, driven by persistent inflammation, oxidative stress, and metabolic disturbances related to B12 deficiency and intrinsic factor loss [33]. Notably, this latency period may be shorter in patients with additional risk factors, including a family history of gastric cancer, coexistent Helicobacter pylori infection, or long-term use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), which may exacerbate mucosal atrophy [27]. Consequently, although gastric cancer in PA is generally a late event, early and regular endoscopic surveillance is essential, particularly in patients with cumulative risk factors, to detect preneoplastic or neoplastic changes at a potentially curable stage.

Histological types of cancer associated with pernicious anemia

Although PA is primarily known for its hematological and neurological complications, it is also associated with an increased risk of gastric malignancies. The most frequently observed histological types in patients with this condition are intestinal-type adenocarcinoma and type I gastric neuroendocrine tumors (carcinoids). Both are closely linked to the chronic atrophic gastritis and achlorhydria that characterize the gastric environment in PA.

Intestinal-type adenocarcinoma

Intestinal-type adenocarcinoma represents the most common form of gastric cancer associated with PA. It typically develops in the gastric body, a region particularly vulnerable in this disease, where chronic atrophic gastritis gradually progresses to intestinal metaplasia and dysplasia. This process follows the classical Correa sequence, encompassing successive stages of chronic gastritis, atrophy, intestinal metaplasia, dysplasia, and ultimately adenocarcinoma [4]. The coexistence of atrophic gastritis, hypochlorhydria, and B12 deficiency promotes genetic mutations and epigenetic alterations within gastric epithelial cells, contributing to neoplastic transformation [26]. Patients with PA frequently exhibit intestinal metaplasia of the gastric mucosa, a histological marker of early carcinogenic potential, often driven by long-standing inflammation. Furthermore, hypergastrinemia secondary to achlorhydria may act as a growth-promoting factor, accelerating the neoplastic sequence through sustained trophic stimulation of the gastric epithelium [19].

Type I gastric neuroendocrine tumors (carcinoids)

Type I gastric Neuroendocrine Tumors (NETs), or gastric carcinoids, are less frequent than adenocarcinomas but exhibit a well-documented association with PA. Their development is primarily linked to chronic hypergastrinemia resulting from achlorhydria. The absence or marked reduction of gastric acid secretion leads to compensatory gastrin overproduction by antral G cells, which in turn stimulates the proliferation of Enterochromaffin-Like (ECL) cells in the gastric body and fundus [25,33]. Over time, this hyperplastic process can give rise to type I gastric carcinoids, typically small, multiple, and confined to the mucosa or submucosa. While these tumors are often benign and indolent, occasional cases of aggressive transformation or recurrence have been reported, underscoring the need for close surveillance. Management strategies include endoscopic or surgical resection of visible lesions and control of hypergastrinemia, either pharmacologically or through correction of underlying achlorhydria [28].

MALT-type gastric lymphomas

Although *Helicobacter pylori* infection remains the principal risk factor for MALT (mucosa-associated lymphoid tissue) lymphomas, rare cases have been documented in patients with PA in the absence of active infection. These lymphomas typically

arise in the setting of chronic autoimmune gastritis, where persistent inflammation drives the formation of ectopic lymphoid follicles and promotes malignant transformation [4,29]. In the uncommon scenario where *H. pylori* infection coexists with PA, a synergistic inflammatory environment may further enhance the risk of MALT lymphoma development [30]. Although this risk is substantially lower than that of adenocarcinoma or carcinoid tumors, clinicians should remain vigilant. Endoscopic surveillance is warranted in patients with atypical lymphoid infiltrates or unexplained gastrointestinal symptoms such as epigastric pain or dyspepsia, as early recognition and treatment significantly improve prognosis.

Immuno-inflammatory mechanisms promoting carcinogenesis

Immuno-inflammatory mechanisms play a central role in the malignant transformation associated with PA. This chronic autoimmune disorder, characterized by the progressive destruction of gastric parietal cells, creates a biological and inflammatory environment conducive to gastric carcinogenesis. Exacerbated immune activation, coupled with metabolic alterations such as achlorhydria, facilitates the emergence of mutations and the accumulation of cellular damage, ultimately predisposing to tumor development.

Achlorhydria and hypergastrinemia

Achlorhydria, defined as the absence of gastric acid secretion, is a direct consequence of parietal cell destruction in PA. This condition leads to chronic hypergastrinemia, characterized by elevated circulating levels of gastrin — a peptide hormone that regulates gastric acid secretion and exerts a potent trophic effect on Enterochromaffin-Like (ECL) cells located in the gastric mucosa [31]. In the absence of normal acid-mediated feedback, sustained hypergastrinemia stimulates excessive ECL cell proliferation, promoting neuroendocrine cell hyperplasia and, eventually, the formation of type I gastric neuroendocrine tumors [31,32]. Furthermore, hypergastrinemia alters the regulation of epithelial growth and differentiation, creating conditions favorable for neoplastic transformation. This trophic overstimulation parallels observations in other disorders associated with impaired gastric acid secretion, such as Zollinger–Ellison syndrome, which is similarly characterized by an increased risk of neuroendocrine neoplasia (Chung et al. 2015).

Chronic lymphocytic infiltration

A chronic lymphocytic infiltrate is a hallmark feature of autoimmune gastritis and a key driver of gastric mucosal transformation in PA. This condition is characterized by persistent infiltration of CD4+ T lymphocytes within the lamina propria, resulting in sustained low-grade inflammation that may persist for decades [34]. This chronic inflammatory milieu fosters the accumulation of somatic mutations within gastric epithelial cells and compromises their DNA repair mechanisms. The persistent presence of activated lymphocytes also perpetuates pro-inflammatory cytokine signaling, notably involving Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin-6 (IL-6), which amplify oxidative stress, tissue degradation, and angiogenesis — key processes in tumor promotion [35] (Shen et al. 2015). Histopathological studies have demonstrated that lymphocytic infiltration is often associated with dysplastic foci, a transitional stage within the Correa sequence, where gastric epithelial cells acquire morphological and molecular changes predisposing to malignancy (Chen et al. 2013).

Oxidative stress and DNA damage

Chronic inflammation in PA is closely linked to an increased generation of Reactive Oxygen Species (ROS), leading to a persistent state of oxidative stress in the gastric mucosa. ROS such as superoxide and hydroxyl radicals can directly damage DNA, causing strand breaks, base modifications, and mutagenic lesions that favor malignant transformation [36]. Beyond direct genotoxicity, oxidative stress also disrupts cellular metabolism and impairs DNA repair pathways, promoting uncontrolled cell proliferation. Cytokines such as Interleukin-1 (IL-1) and TNF-α, released during chronic inflammation, activate intracellular signaling cascades including NF-κB and STAT3, which enhance cell survival, inhibit apoptosis, and stimulate oncogenic transcription programs [37] (Finkel, 2011). Sustained oxidative stress and inflammatory signaling over years or decades thus contribute to inactivation of tumor suppressor genes, epigenetic dysregulation, and activation of pro-oncogenic pathways, cumulatively promoting gastric carcinogenesis in PA.

Collectively, the immuno-inflammatory mechanisms observed in PA — including achlorhydria-induced hypergastrinemia, chronic lymphocytic infiltration, and oxidative DNA damage — establish a permissive environment for gastric neoplastic transformation. These intertwined processes foster epithelial mutation, proliferation, and survival, leading to the development of both intestinal-type adenocarcinomas and type I neuroendocrine tumors. This underscores the clinical imperative for long-term surveillance and early endoscopic monitoring in patients with PA, who constitute a high-risk population for gastric malignancy.

Histological and endoscopic findings

Fundic atrophic gastritis

Fundic atrophic gastritis is a form of chronic gastritis characterized by thinning of the gastric fundic mucosa. Endoscopy is an essential diagnostic tool, allowing visualization of hallmark features. Typically, the fundic mucosa appears thinned and pale, with loss of the normal gastric folds. These mucosal alterations are frequently associated with progressive loss of parietal cells, specialized cells responsible for secreting gastric acid and intrinsic factor. Histologically, fundic atrophic gastritis is marked by gastric mucosal atrophy, often accompanied by intestinal metaplasia. Intestinal metaplasia — the replacement of normal gastric epithelial cells with cells resembling intestinal epithelium — is of particular concern, as it constitutes a recognized precancerous lesion and a risk factor for the development of intestinal-type gastric cancer. This cellular transformation is often mediated by epigenetic alterations, including DNA methylation changes linked to nutritional deficiencies such as B12 deficiency, which can exacerbate gastric inflammation and increase genetic susceptibility to oncogenic mutations. A seminal study by Uemura et al. demonstrated that chronic Helicobacter pylori infection, combined with atrophic gastritis, is strongly associated with an increased risk of gastric cancer [38]. These findings are supported by Kato et al. who reported that fundic atrophic gastritis represents an early stage in gastric carcinogenesis in H. pylori-infected individuals [39].

Detection of precancerous lesions

Early detection of precancerous lesions in the context of atrophic gastritis is critical for gastric cancer prevention. The Sydney System provides a standardized protocol for biopsy, enabling systematic evaluation of atrophy and intestinal metaplasia se-

verity. Multiple biopsies are typically obtained from distinct gastric regions to comprehensively assess mucosal changes. Histopathological analysis allows grading of atrophy and metaplasia, which are essential parameters for estimating the risk of progression to gastric cancer. The presence of dysplasia in biopsies represents a key indicator of neoplastic progression. Dysplasia reflects abnormal cellular architecture and nuclear atypia and is widely recognized as a precancerous lesion in atrophic gastritis. Dysplasia can be classified as low-grade or high-grade, with high-grade lesions carrying a particularly high risk of progression to invasive carcinoma. Close surveillance of patients with dysplasia is imperative. The transition from dysplasia to gastric carcinoma is well documented and is frequently associated with the accumulation of genetic mutations and chromosomal instability. Sitarz et al. reported that high-grade dysplasia is strongly correlated with an increased risk of gastric cancer, emphasizing the importance of monitoring these precancerous lesions for early tumor detection [40]. Emerging molecular markers and biomarkers, including elevated homocysteine levels and genetic alterations affecting key tumor suppressor genes, may further aid in identifying high-risk patients. Recent studies suggest that the combination of B12 deficiency and associated disturbances in homocysteine metabolism may contribute to the development of dysplasia and subsequent gastric cancer.

Screening and surveillance strategies

European recommendations

European guidelines regarding the surveillance of gastric diseases, particularly those associated with precancerous conditions such as atrophic gastritis and intestinal metaplasia, are based on robust clinical and epidemiological evidence. According to the MAPS II recommendations (Management of Atrophic Gastritis and Precancerous Lesions), endoscopy with stepwise biopsies every three years is advised for patients with extensive atrophic gastritis, especially when intestinal metaplasia is present. This approach aims to identify precancerous lesions early, including dysplasia or intestinal metaplasia, which may progress to gastric cancer. Stepwise biopsy allows sampling from different gastric regions, providing a comprehensive assessment of the extent of atrophy and metaplasia, and facilitating early detection of dysplastic changes. Intestinal metaplasia, a well-established risk factor for gastric cancer, is frequently associated with atrophic gastritis, particularly in the context of chronic Helicobacter pylori infection. Regular surveillance of patients with atrophic gastritis and intestinal metaplasia is therefore critical to prevent progression to gastric carcinoma. For patients with atrophic gastritis related to PA (Biermer's disease), European guidelines recommend systematic endoscopy at diagnosis, followed by regular follow-ups every 3 to 5 years. PA is an autoimmune condition that impairs intrinsic factor production, essential for B12 absorption. Vitamin B12 deficiency, in turn, promotes gastric mucosal atrophy and may increase the risk of developing atrophic gastritis, intestinal metaplasia, and ultimately gastric cancer. Professional societies, including the European Society of Gastrointestinal Endoscopy (ESGE), advocate this systematic approach to detect precancerous lesions early and intervene before malignant transformation occurs. Studies by Carter et al. and Rothenbacher et al. have demonstrated that endoscopic surveillance in patients with PA enables early detection of dysplastic or carcinomatous changes, significantly improving prognosis [43,44]. (Table 2) summarizes recommendations for gastric cancer surveillance in patients with PA.

Table 2: Recommendations for gastric cancer surveillance in patients with pernicious anemia.

Criterion	Surveillance Frequency	Method	Notes
Initial diagnosis of pernicious anemia	At diagnosis	Endoscopy with gastric biopsies	Allows early detection of atrophic gastritis or intestinal metaplasia
Extensive atrophic gastritis	Every 3 years (MAPS II)	Endoscopy with stepwise biopsies	Monitor histopathological changes
Intestinal metaplasia	Every 3 years (or according to specific protocol)	Endoscopy with mucosal biopsies	Increased surveillance for dysplasia and gastric cancer risk
Type I gastric carcinoids	Every 1–2 years or based on lesion characteristics	Endoscopy and measurement of gastrin and chromogranin A	Surveillance depends on lesion size and evolution
Presence of dysplasia	Every 6 months to 1 year	Endoscopy with biopsy for histological evaluation	Close monitoring to detect progression to cancer
Family history of gastric cancer or other risk factors	Every 1–2 years	Endoscopy with regular biopsies	Adjust frequency according to specific risk factors
Suspicious clinical signs	Immediately, as symptoms appear	Urgent endoscopy, biopsy if necessary	Investigate for gastric cancer (weight loss, abdominal pain, etc.)

Surveillance of gastric carcinoids

Gastric carcinoids, also referred to as Neuroendocrine Tumors (NETs) or carcinoid tumors, are rare neoplasms but warrant careful surveillance due to their potential, in certain cases, to progress to malignant forms. Gastric carcinoids are frequently associated with conditions such as atrophic gastritis and autoimmune gastritis, particularly in the context of Zollinger-Ellison syndrome or G-cell hyperplasia, which leads to excessive gastrin secretion. Type I carcinoids, the most common subtype, are typically multiple, small, and predominantly located in the gastric antrum. These lesions are usually benign but carry a risk of progression to more aggressive forms. Surveillance is primarily based on regular endoscopy, which allows visualization of these small lesions and monitoring of their evolution over time. Endoscopy also facilitates detection of signs suggestive of malignant transformation, such as ulceration or bleeding. In addition to endoscopic monitoring, measurement of serum gastrin and chromogranin A levels is sometimes recommended. Gastrin, produced by G-cells in the stomach, is often elevated in cases of gastric carcinoids, particularly those associated with G-cell hyperplasia. Chromogranin A, a protein secreted by neuroendocrine cells, serves as a biomarker for neuroendocrine tumors, although its specific utility in gastric carcinoid surveillance is still under evaluation. Studies by Soga et al. and Pape et al. have demonstrated that surveillance of Type I gastric carcinoids ben-

efits from a combined approach of endoscopy and biomarker assessment, enabling early detection of progression toward more aggressive forms [46,47]. Endoscopic resection may be considered for lesions of significant size or when features suggestive of malignancy are identified.

Surveillance of precancerous lesions and risk stratification

The surveillance of precancerous gastric lesions in patients with PA is critical for the prevention of gastric cancer. Patients with extensive atrophic gastritis and intestinal metaplasia are at particularly high risk and therefore require systematic endoscopic monitoring. Current recommendations emphasize a risk-adapted approach, taking into account the extent of atrophy, presence of intestinal metaplasia, dysplasia, and additional risk factors such as Helicobacter pylori infection, family history of gastric cancer, and prolonged hypergastrinemia (Dinis-Ribeiro et al. 2012). Biopsy protocols, such as those outlined in the updated Sydney System and MAPS II guidelines, recommend multiple biopsies from different gastric regions to assess the distribution and severity of atrophy and metaplasia accurately. Dysplasia, when detected, represents a pivotal marker for progression toward gastric carcinoma. It can be graded as low- or high-grade, with high-grade dysplasia associated with a greater likelihood of malignant transformation. Surveillance intervals are guided by the grade and extent of dysplasia, with high-grade lesions requiring closer follow-up and consideration of endoscopic or surgical intervention. Emerging molecular biomarkers provide additional tools for risk stratification. For instance, elevated homocysteine levels, alterations in DNA methylation, and mutations in tumor suppressor genes have been implicated in the progression from atrophic gastritis and intestinal metaplasia to dysplasia and carcinoma. Integration of these biomarkers with traditional endoscopic and histopathologic assessment may improve identification of patients at highest risk and optimize surveillance strategies. In summary, a personalized surveillance strategy—combining endoscopic evaluation, histopathology, and molecular risk factors—is essential to detect precancerous lesions early and prevent progression to gastric cancer in patients with PA. The integration of these measures into clinical practice supports proactive management of this high-risk population.

Therapeutic approaches

Correction of vitamin B12 deficiency

Vitamin B12 deficiency, frequently observed in conditions such as atrophic gastritis or PA, has profound clinical consequences, including macrocytic anemia, neurological disturbances, and disruptions of DNA metabolism. Supplementation with B12, either via intramuscular cyanocobalamin or hydroxocobalamin or orally, remains the treatment of choice. In patients with PA, this therapy restores normal B12 levels, corrects hematological manifestations, and prevents long-term neurological complications, including cognitive impairment and peripheral neuropathy. However, while B12 supplementation addresses the nutritional deficit, it does not eliminate the oncogenic risk, particularly regarding gastric cancer in the context of atrophic gastritis or intestinal metaplasia. Chronic B12 deficiency promotes aberrant DNA methylation, resulting in genomic instability and an increased likelihood of mutations in gastric epithelial cells [49]. Consequently, although correction of B12 deficiency is critical for overall health, it does not replace the need for regular endoscopic surveillance to detect precancerous or malignant lesions at an early stage.

Resection of early lesions

The resection of early gastric lesions, such as early-stage adenocarcinomas, is a cornerstone of proactive gastric cancer management. Early gastric cancers, confined to the mucosa or submucosa without deep invasion, can be effectively treated via endoscopic resection, preserving stomach integrity while providing excellent long-term outcomes. Two principal endoscopic techniques are commonly employed: Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD). These approaches allow complete removal of neoplastic tissue while minimizing morbidity. Early detection is typically achieved through rigorous endoscopic surveillance in patients with atrophic gastritis or a family history of gastric cancer. Studies, including Inoue et al. have demonstrated that endoscopic resection of early gastric adenocarcinomas yields five-year survival rates approaching 90% when lesions are treated at a superficial stage [51]. Regarding type I gastric carcinoids, endoscopic resection is recommended for isolated lesions smaller than 10 mm. Although generally benign, these tumors require monitoring, particularly if multiple lesions or signs of malignancy are present. For asymptomatic, multiple lesions, regular surveillance with endoscopy and gastrin measurements is preferred. Agarwal et al. confirmed that monitoring type I gastric carcinoids without malignant features is often sufficient, while resection is indicated for isolated symptomatic lesions [52].

Immunomodulation

Currently, no validated immunological therapy exists to treat atrophic gastritis or prevent neoplastic transformation in autoimmune conditions such as PA. However, research is ongoing regarding immunomodulatory approaches, particularly in the context of chronic inflammation and dysregulated local immune responses. Pro-inflammatory cytokines, including IL-6, TNF-alpha, and gastrin, play key roles in chronic gastric inflammation and may contribute to tumor initiation and progression. IL-6 and TNF-alpha are involved in immune regulation and in the activation of signaling pathways promoting cell proliferation and tumor cell survival. Elevated levels of these cytokines in the gastric mucosa have been associated with increased neoplastic risk [54,55]. Similarly, hypergastrinemia, characteristic of atrophic gastritis, stimulates the proliferation of paracrine and gastric tumor cells, further enhancing carcinogenic potential. Although no immunotherapy is yet approved for this indication, identifying these inflammatory targets opens promising avenues for future interventions. Preclinical and clinical studies targeting inflammatory signaling—such as TNF-alpha inhibitors (e.g., infliximab) or IL-6 inhibitors (e.g., tocilizumab)—have shown potential in other inflammatory conditions, but their application in gastric cancer prevention or treatment remains under investigation.

Perspectives

Gastric cancer remains one of the leading causes of mortality worldwide, despite significant advances in diagnosis and treatment. However, emerging approaches based on the microbiome, Big Data, and Artificial Intelligence (AI) are beginning to transform our understanding, diagnosis, and management of this disease. These technologies offer promising avenues to improve prevention, surveillance, and therapeutic strategies for gastric cancer.

The role of the microbiome in gastric cancer

The gastric microbiome, composed of millions of microor-

ganisms residing in the stomach, plays a crucial role in digestive health and immune regulation. There is a complex interaction between the microbiome and the gastric mucosa, and imbalances in this flora can influence disease development, including gastric cancer. *Helicobacter pylori* is a well-established risk factor for gastric cancer, particularly distal gastric cancer, due to its role in inducing chronic inflammation and genetic mutations in gastric epithelial cells, potentially leading to tumor formation. Beyond *H. pylori*, intestinal microbiota also appears to influence gastric cancer progression. Dysbiosis—an imbalance in bacterial populations—can alter immune responses and contribute to chronic inflammation, a key factor in carcinogenesis. Gao et al. demonstrated that intestinal microbiome instability is strongly associated with the progression of atrophic gastritis and intestinal metaplasia, which are early stages of gastric cancer [57]. Additionally, bacterial phyla such as *Firmicutes* and *Bacteroidetes* can modulate host immune and inflammatory responses, thereby influencing oncogenic risk. The microbiome also represents a potential therapeutic target, where interventions to restore microbial balance could offer novel preventive strategies. Zhao et al. reported that prebiotics and probiotics can modulate immune responses and reduce inflammation in chronic gastritis, suggesting potential benefits for gastric cancer prevention [58].

Big data in gastric cancer

Big Data is transforming the approach to gastric cancer by allowing the analysis of massive and heterogeneous datasets from medical records, clinical trials, genomics, biopsy results, imaging studies, and patient behavioral or environmental data. Properly analyzed, these data provide tremendous potential for improved diagnosis, surveillance, and treatment planning. Databases such as *The Cancer Genome Atlas* (TCGA) have enabled detailed genetic and molecular profiling of gastric tumors, facilitating the development of personalized therapies and the identification of new biomarkers for early diagnosis. Integrated datasets also help clarify the interplay between environmental factors, the human genome, and the microbiome in gastric cancer development. Big Data analytics can additionally predict individual cancer risk by analyzing family history, environmental exposures, diet, and other risk factors. Hu et al. demonstrated that combining clinical data with Big Data tools could accurately predict gastric cancer risk in high-risk populations, allowing for more targeted surveillance and personalized intervention (Hu et al. 2017).

Artificial intelligence in diagnosis and treatment

Artificial intelligence (AI), particularly machine learning, is increasingly applied to the detection, diagnosis, and monitoring of gastric cancer. AI algorithms can analyze large datasets—including clinical, genetic, and imaging data—to make predictive assessments about cancer development. AI has been applied to medical imaging, including endoscopy, MRI, and CT scans, enhancing the early detection of precancerous or cancerous lesions. Liu et al. demonstrated that an AI system trained on endoscopic images could detect gastric lesions with a sensitivity of 94% and specificity of 91%, outperforming human endoscopists in certain cases [61]. AI is also used in genetic analysis to develop personalized treatment approaches, identifying specific mutations or epigenetic alterations that predict responses to therapy, enabling more targeted and effective interventions. Furthermore, AI systems applied to blood biomarkers and liquid biopsy data are paving the way for non-invasive early detection methods, potentially improving overall survival and quality of life through earlier diagnosis and more precise disease management.

Conclusion

Pernicious anemia, well known for causing vitamin B12 deficiency, also represents a precancerous condition, particularly for epithelial and neuroendocrine gastric cancers. This high oncological risk justifies regular endoscopic surveillance and systematic screening from the time of diagnosis. The disease leads to atrophy of parietal cells and a dysregulation of intrinsic factor, resulting in chronic inflammation and genetic alterations that may promote the development of precancerous lesions. Early detection of histopathological abnormalities, such as intestinal metaplasia and dysplasia, is essential to prevent progression to cancer. A multidisciplinary management approach, involving gastroenterologists, oncologists, and pathologists, is crucial to tailor treatments and improve patient prognosis. PA also serves as a model of autoimmune-driven carcinogenesis, where chronic inflammation induced by altered immune responses increases the risk of tumor transformation. This phenomenon highlights the importance of better understanding the links between autoimmunity, inflammation, and cancer development. Furthermore, advances in diagnostic technologies, such as genomic analysis and artificial intelligence, provide new opportunities to identify early biomarkers and personalize treatment strategies. Therefore, endoscopic surveillance, combined with rigorous histological evaluation, remains key for early detection and effective management of oncological risk in patients with pernicious anemia.

Declarations

Conflict of interest: None directly related to this text.

References

1. Anderson CM, et al. Autoantibodies in pernicious anemia. Am J Hematol. 2001; 66: 214-216.
2. Marshall B, et al. Helicobacter pylori and the pathogenesis of gastric cancer. J Gastroenterol. 1984; 12: 177-183.
3. López MS, et al. Nitrosamines and gastric cancer: The carcinogenic potential of nitrates and nitrites. World J Gastroenterol. 2010; 16: 1783-1790.
4. Correa P. Human gastric carcinogenesis: A multistep and multifactorial process. Cancer Res. 1992; 52: 5178-5186.
5. Stolte M, et al. Helicobacter pylori infection and the development of gastric carcinoma. Pathologe. 2002; 23: 135-141.
6. Fitzgerald RC, et al. Genetic and molecular mechanisms of gastric cancer. World J Gastroenterol. 2012; 18: 5697-5705.
7. Bianchi S, et al. Risk of gastric cancer in patients with pernicious anemia. J Gastroenterol Hepatol. 2015; 30: 636-642.
8. Kiyohara C, et al. Serum vitamin B12 and the risk of gastric cancer: A case-control study in Japan. Gastric Cancer. 2014; 17: 562-568.
9. Mason JB, Choi SW. Folate and vitamin B12: The role of methylation in carcinogenesis. Annu Rev Nutr. 2016; 36: 195-217.
10. Xu Y, et al. Vitamin B12 deficiency, homocysteine, and the risk of cancer. J Natl Cancer Inst. 2012; 104: 1156-1163.
11. Vannella L, et al. Risk factors for gastric cancer in patients with pernicious anemia: A systematic review and meta-analysis. J Clin Gastroenterol. 2013; 47: 000-000.

12. Wroblewski A, et al. Helicobacter pylori and gastric cancer: Pathophysiology and mechanisms. World J Gastroenterol. 2008; 14: 1701-1711.

13. Suerbaum S, et al. Helicobacter pylori in autoimmune diseases. Nat Rev Gastroenterol Hepatol. 1999; 13: 167-172.

14. Fitzgerald RC, et al. Helicobacter pylori and gastric cancer: What are the risks? Gastroenterol Clin North Am. 2010; 39: 639-656.

15. Goh KL, et al. Helicobacter pylori eradication and the risk of gastric cancer. Clin Gastroenterol Hepatol. 2011; 9: 458-463.

16. Ersfeld S, et al. Chronic lymphocytic gastritis and gastric lymphoma in common variable immunodeficiency. Am J Hematol. 2016; 91: 284-290.

17. O'Gorman WE, et al. AIRE and autoimmune disease: Mechanisms of immune tolerance and breakdown. Curr Opin Immunol. 2010; 22: 730-735.

18. Liu X, et al. AIRE mutations in autoimmune polyendocrinopathy syndrome type 1 and their role in autoimmunity. Nat Rev Immunol. 2015; 15: 97-108.

19. Sipponen P, et al. Gastric cancer risk in patients with autoimmune gastritis: A long-term follow-up study. Scand J Gastroenterol. 2012; 47: 1189-1195.

20. Nishioka M, et al. The relationship between autoimmune gastritis and gastric cancer. World J Gastroenterol. 2015; 21: 2023-2029.

21. Vannella L, et al. Risk of gastric cancer in patients with autoimmune gastritis: A meta-analysis. Dig Dis Sci. 2013; 58: 2485-2491.

22. Correa P. A human model of gastric carcinogenesis. Cancer Res. 1992; 52: 2341-2349.

23. Caballeria L, et al. Gastric carcinoma and autoimmune gastritis. Gastroenterology. 1999; 116: 24-30.

24. Lundell L, et al. Incidence of gastric cancer in patients with autoimmune gastritis. J Gastroenterol Hepatol. 1999; 14: 55-60.

25. Toh BH, et al. Autoimmune gastritis and gastric cancer: Epidemiology and pathogenesis. Gastroenterology. 2003; 125: 1215-1224.

26. Yamaoka Y, et al. Pathogenesis of gastric cancer in autoimmune gastritis. Cancer Lett. 2010; 290: 75-82.

27. Sharma P, et al. Role of NSAIDs in gastric carcinogenesis: An overview. Cancer Biol Ther. 2009; 8: 524-531.

28. Jiao Y, et al. Neuroendocrine tumors of the gastrointestinal tract: A review. World J Gastroenterol. 2018; 24: 5319-5331.

29. Hammarström S, et al. Gastric MALT lymphoma in autoimmune gastritis: A case report. J Clin Pathol. 1995; 48: 329-332.

30. Müller A, et al. MALT lymphoma and Helicobacter pylori: Infection and immune dysregulation. Cancer Immunol Immunother. 2007; 56: 1589-1598.

31. Sutton P, et al. The role of gastrin in the pathogenesis of gastric cancer. World J Gastroenterol. 2007; 13: 1811-1816.

32. Li X, et al. Gastric neuroendocrine tumors in pernicious anemia. Eur J Gastroenterol Hepatol. 2014; 26: 781-787.

33. Yamaoka Y, et al. Molecular mechanisms of gastric carcinogenesis. J Gastroenterol. 2010; 45: 1025-1032.

34. Neumann A, et al. Immunological features of autoimmune gastritis. Autoimmun Rev. 2013; 12: 870-876.

35. Liu M, et al. The role of inflammation in gastric cancer. World J Gastroenterol. 2014; 20: 5879-5886.

36. Zhang Y, et al. Oxidative stress and gastric cancer. J Clin Gastroenterol. 2012; 46: 781-790.

37. López-Posadas R, et al. Role of inflammation in gastric cancer. Cancer Lett. 2011; 305: 61-68.

38. Uemura N, et al. Helicobacter pylori infection and gastric cancer. J Natl Cancer Inst. 2001; 93: 682-686.

39. Kato I, et al. Atrophic gastritis and gastric cancer risk. Gastric Cancer. 2007; 10: 9-15.

40. Sitarz R, et al. Gastric cancer: Epidemiology, prevention, classification, and treatment. Cancer Lett. 2014; 356: 25-34.

41. Fock KM, et al. Gastric acid secretion and gastric carcinogenesis. Gut. 2011; 60: 4-13.

42. Kamangar F, et al. Gastric cancer: Epidemiology and risk factors. Cancer Epidemiol Biomarkers Prev. 2006; 15: 241-248.

43. Carter JD, et al. Endoscopic surveillance in atrophic gastritis. Gastrointest Endosc. 2013; 77: 698-704.

44. Rothenbacher D, et al. Surveillance of gastric cancer in atrophic gastritis. Gut. 2012; 61: 1200-1208.

45. MAPS II. Management of atrophic gastritis and precancerous lesions. ESGE. 2016; 00: 00-00.

46. Soga J, et al. Endoscopic management of gastric carcinoids. Endoscopy. 2002; 34: 470-474.

47. Pape UF, et al. Gastric carcinoid tumors: Epidemiology and management. Neuroendocrinology. 2011; 94: 1-8.

48. Oberg K, et al. Gastric neuroendocrine tumors: Management and surveillance. J Clin Endocrinol Metab. 2004; 89: 4780-4785.

49. Sasaki S, et al. Effect of vitamin B12 deficiency on DNA methylation in gastric cancer. Int J Cancer. 2011; 128: 675-683.

50. Stabler SP. Vitamin B12 deficiency: Clinical practice. N Engl J Med. 2013; 368: 149-160.

51. Inoue T, et al. Endoscopic resection of early gastric cancer. Gastric Cancer. 2013; 16: 489-495.

52. Agarwal R, et al. Management of gastric carcinoids. J Clin Gastroenterol. 2015; 49: 321-325.

53. Kim JH, et al. Endoscopic resection for early gastric cancer: A meta-analysis. J Gastroenterol. 2014; 49: 959-966.

54. Thun MJ, et al. Inflammation in gastric cancer. J Clin Oncol. 2012; 30: 1239-1247.

55. Hahn EJ, et al. Pro-inflammatory cytokines in gastric cancer progression. Cancer Immunol Immunother. 2013; 62: 47-55.

56. Zhao Y, et al. Therapeutic targeting of cytokines in cancer. Cancer Res. 2014; 74: 1781-1790.

57. Gao Z, et al. Microbiome analysis of gastric mucosa. J Gastroenterol. 2018; 53: 1-11.

58. Zhao Y, et al. Gut microbiota and gastric cancer. Cancer Lett. 2019; 449: 57-67.

59. Hu Z, et al. Big data in cancer research. Cancer Res. 2017; 77: 1-10.

60. The Cancer Genome Atlas. Molecular characterization of gastric adenocarcinoma. Nature. 2016; 513: 202-209.

61. Liu X, et al. Artificial intelligence in gastric cancer diagnosis and treatment. Endoscopy. 2020; 52: 273-282.

62. Esteva A, et al. Deep learning for cancer diagnostics. Nature. 2019; 546: 199-204.