REVIEW

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DIAGNOSTIC AND THERAPEUTIC APPROACHES IN THE TREATMENT OF GASTRIC CANCER – A SCOPING REVIEW

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Abstract. *Gastric carcinoma poses a significant clinical challenge and remains one of the leading causes of cancer-related mortality worldwide. Accurate classification of these tumors based on their histology, anatomical location, and molecular characteristics is essential, as it dictates both prognosis and therapeutic strategy.* ***Objective*****:** *to review the key classification systems that underpin the current understanding and treatment of gastric cancer, and to analyze new approaches to diagnosis and treatment through a systematic review of scientific publications.* ***Materials and Methods:*** *we conducted a scoping review by searching for scientific publications in various sources – databases and printed literature, articles, textbooks, monographs, etc.* ***Results and Discussion:*** *Lauren's histological classification distinguishes between intestinal and diffuse types, which have different etiologies and prognoses. The anatomical location, especially the distinction between cardia and non-cardia cancer, is also important. The evolving understanding of its biology, including the key role of H. pylori, hereditary syndromes, such as HDGC, and the clinical significance of TCGA molecular subtypes, has been changing the epidemiological landscape and shaping the current paradigm of multidisciplinary, multimodal treatment. Radical surgical treatment and adequate lymph node dissection determine the outcome of the disease. Advances in perioperative systemic treatments and a personalized approach based on biomarkers, such as MSI status for immunotherapy, improve treatment outcomes.*

Key words: *gastric cancer, H. Pylori, pathoanatomy, staging, treatment*

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INTRODUCTION

Gastric carcinoma (GC) is the fifth most common cancer and the fourth leading cause of cancer-related deaths worldwide. According to statistics from 2020, over 1,089,000 new cases and 769,000 deaths were reported, highlighting its significant global burden [5, 6, 8]. There is a clear geographical variation in the incidence of GC. The most severely affected countries are those in East Asia (Japan, Korea, China), which is associated with the high seroprevalence of *Helicobacter pylori (H. pylori)* infection. In contrast, the incidence is significantly lower in Western Europe and North America [6]. The main age trends show that while the overall incidence of non-cardia gastric cancer is declining due to improved food storage and control of *H. pylori*, there has been an alarming increase in incidence among younger populations (under 50 years of age) in some Western countries, such as the US and the UK [5, 6, 9, 11]. Early-onset gastric cancer (EOGC) is defined as a diagnosis made at or before the age of 45 and accounts for about 10% of all GC cases. This subgroup is of particular clinical interest because it is often biologically more aggressive, is detected at an advanced stage, and appears to be less dependent on traditional environmental carcinogens. This suggests a stronger influence of genetic factors in its etiology.

Gastric carcinogenesis is a multifactorial process involving complex interactions between environmental factors, individual host characteristics, and genetic predisposition. *H. pylori* infection is the most significant risk factor for GC, recognized as a class 1 carcinogen and responsible for nearly 90% of distal gastric cancers [1, 6, 8, 12]. The model of carcinogenesis caused by *H. pylori* is described by Correa's cascade, which progresses from chronic gastritis to atrophy, intestinal metaplasia, and finally carcinoma [13]. The Epstein-Barr virus is another established infectious risk factor, associated with approximately 9% of gastric cancers. It usually affects the proximal stomach [4, 14, 15].

A variety of dietary and lifestyle factors have been identified as major risk factors for GC. Diet: high intake of salt and salt-preserved foods, smoked foods, and N-nitroso compounds increases the risk [16, 17]. A diet low in fruits, vegetables, and fiber is also a risk factor, while high intake has a protective effect [3, 8, 18-20]. Smoking and alcohol: both tobacco use and alcohol consumption are confirmed risk factors for gastric cancer. Obesity and GERD: A high body mass index (obesity) and chronic gastroesophageal reflux disease (GERD) increase the risk of cancer of the cardia and gastroesophageal junction [3, 6].

Other conditions have also been identified as ones that pose an increased risk for the development of gastric cancer. Chronic atrophic gastritis and intestinal metaplasia – a key step in the Correa cascade, often resulting from chronic *H. pylori* infection [7, 21]. Pernicious anemia increases the risk of intestinal-type gastric cancer [3, 7]. Remnant stomach – bile reflux into the stomach remnant after certain gastric surgeries increases the long-term risk of cancer. Gastric polyps, especially adenomas, have the potential for malignant transformation.

Some hereditary syndromes predispose to the development of gastric cancer – hereditary diffuse gastric cancer (HDGC) is one of the most significant genetic predispositions. It is caused by germline mutations in the *CDH1* (E-cadherin) gene [13, 14]. The lifetime risk of developing diffuse gastric cancer is high (67% for men and 83% for women up to 80 years of age), as is the risk of lobular breast cancer in women (60%) [14]. Due to the infiltrative nature of the cancer, prophylactic total gastrectomy is the recommended treatment for carriers of pathogenic *CDH1* mutations [23-26]. Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer), caused by mutations in mismatch repair (MMR) genes, carries an increased risk of stomach cancer, estimated at 0.2-13% [32].

Adenocarcinoma is the most common malignant disease of the stomach. The Lauren classification system is widely used and divides gastric adenocarcinoma into two main histological subtypes, each with different clinical and molecular characteristics: **intestinal type**, usually associated with a stepwise carcinogenic process known as the Correa cascade, which begins with chronic inflammation, such as gastritis caused by *H. pylori* [1, 2]; **diffuse type**: characterized by poorly cohesive cells, often including signet-ring cells. This type is associated with a poorer prognosis and different molecular characteristics,

such as mutations in the *CDH1* gene [3, 4]. There also are mixed histological types which exhibit characteristics of both the intestinal and diffuse types.

It is important to distinguish between cancers arising in the cardia (proximal stomach) and those in the non-cardia (distal stomach). In contrast, cardia tumors, which are often associated with obesity and gastroesophageal reflux disease (GERD), continue to pose a serious challenge [5, 6].

The Siewert classification is crucial for tumors affecting the gastroesophageal junction (GEJ), as it determines whether they are staged and treated according to guidelines for esophageal or gastric cancer. This is based on the location of the tumor epicenter [7]. **Siewert Type I:** adenocarcinoma of the distal esophagus, in which the tumor epicenter is located 1 to 5 cm above the gastroesophageal junction. These tumors are staged as esophageal cancer [7, 8]. **Siewert Type II:** true adenocarcinoma of the cardia, in which the epicenter is located within 1 cm above or 2 cm below the gastroesophageal junction. According to the 8th edition of the American Joint Committee on Cancer (AJCC), these tumors are also staged as esophageal cancer [7, 8]. **Siewert Type III:** subcardial adenocarcinoma, in which the epicenter is located 2 to 5 cm below the gastroesophageal junction. These tumors are staged and treated as gastric cancer [7, 8].

The understanding of stomach cancer has evolved from purely histological to molecular. Modern classifications based on genomic and molecular signatures allow for more precise stratification of patients and targeting of therapy. The development of intestinal-type gastric adenocarcinoma is characterized by a progressive accumulation of genetic and epigenetic changes, often following the Correa pathway [2, 13]. This process leads to tumors with high levels of chromosomal instability (CIN), characterized by aneuploidy (changes in chromosome number) and frequent mutations in tumor suppressor genes, such as TP53 [4, 15, 27]. Diffuse-type gastric cancer often arises without a clear preceding lesion and is molecularly distinct. It is strongly associated with germline or somatic inactivation of the E-cadherin (*CDH1*) gene, leading to loss of intercellular adhesion and allowing an infiltrative growth pattern [1, 22, 28].

The Cancer Genome Atlas (TCGA) project defines four molecular subtypes of gastric cancer that are clinically relevant for prognosis and treatment selection [5, 15, 27, 28, 29]: **1. Chromosomally unstable (CIN):** this subtype is the most common (~50%) and often corresponds to the Lauren histological type. It is associated with aneuploidy and TP53 mutations and shows relative sensitivity to conventional chemotherapy. **2. Microsatellite unstable (MSI):** it accounts for ~22% of cases and occurs due to a deficiency in the mismatch repair (MMR) system. It is characterized by a high mutation burden in the tumor and high sensitivity to immune checkpoint inhibitors (ICI) [30, 31]. **3. Epstein-Barr virus (EBV) positive:** it accounts for ~9% of cases, characterized by DNA hypermethylation and frequent overexpression of PD-L1/L2, which also suggests sensitivity to ICI [30, 31]. **4. Genomically stable (GS):** this subtype accounts for ~20% of cases and is often associated with diffuse histology and RHOA mutations. Patients with this subtype benefit least from standard adjuvant chemotherapy [30].

The tumor microenvironment (TME), consisting of immune cells, fibroblasts, and signaling molecules, is critical for tumor initiation and progression [33]. Chronic inflammation caused by factors such as *H. pylori* activates transcription factors (NF-κB, STAT3) that promote cell survival and angiogenesis [34-37]. Specific molecular signals, such as SDF-1/CXCR4, facilitate peritoneal metastasis [33, 38].

Gastric cancer metastasizes in four main ways: **local invasion:** direct spread through the stomach wall to adjacent organs [5]; **lymphatic spread:** the most common route, involving first the peri-gastric (D1) and then the extra-peri-gastric (D2) lymph nodes [14, 39]; **peritoneal spread (carcinomatosis):** a common (15-32%) and often hidden cause of treatment failure [40]; **hematogenous spread:** mainly to the liver, lungs, and bones.

Eponymous signs of metastatic disease: the presence of any of these signs on physical examination is pathognomonic for metastatic disease (M1) and usually excludes the possibility of radical treatment: **Virchow's node:** enlarged left supraclavicular lymph node indicating widespread lymphatic metastasis through the thoracic duct [7, 13, 41]; **Sister Mary Joseph node (SMJN):** a metastatic node in the umbilical region, indicating diffuse peritoneal involvement and associated with a very poor prognosis [41, 42]; **Krukenberg tumor:** metastases in the ovaries, histologically characterized by signet-ring cells, most often with primary origin in the stomach.

The AJCC TNM system is the universally accepted standard for classifying the extent of disease spread. Macroscopic classification (Borrmann) is used to describe the macroscopic appearance of advanced gastric cancer. Borrmann type IV, known as *linitis plastica*, is a diffusely infiltrative type in which the stomach wall becomes rigid and inextensible, which is associated with a poor prognosis [43]. Early gastric cancer (EGC) is defined as a tumor confined to the mucosa or submucosa (T1), regardless of lymph node status [14]. In

contrast, advanced gastric cancer infiltrates the muscular layer (muscularis propria) or deeper structures (T2-T4). Key microscopic features, such as Lauren histological type (intestinal versus diffuse), and the presence of signet-ring cells have significant prognostic value and influence therapeutic decisions [44].

The TNM system, according to the 8th edition of the AJCC, evaluates three main components to determine the stage of cancer [4]: **T (Tumor):** this category describes the depth of tumor invasion through the five layers of the stomach wall. The categories range from Tis (carcinoma *in situ*) to T4b, which means invasion into adjacent structures [45]; **N (Nodes):** this category quantifies the number of regional lymph nodes containing metastases. Categories range from N0 (no metastases) to N3b (≥16 affected nodes). The degree of lymph node involvement is a powerful prognostic factor, often more influential than the T stage [46]; **M (Metastases):** this category describes the presence of distant metastases. M0 means no distant metastases, and M1 means the presence of distant metastases. Crucially, the presence of positive peritoneal cytology (CY1) is classified as M1 disease [47]. The combination of T, N, and M categories determines the stage, which is the most accurate predictor of prognosis [14].

Early gastric cancer (EGC) is often asymptomatic or presents with vague symptoms, such as epigastric pain, indigestion, and anorexia. These complaints are often confused with benign conditions, leading to delayed diagnosis [17, 23, 57, 58]. Persistent, worsening, vague abdominal pain is a constant symptom, even in the early stages of the disease [48]. Unexplained weight loss is a common sign of advanced disease [48]. Tumors in the pyloric region cause obstruction, manifesting as constant nausea and vomiting of undigested food after eating [49]. Tumors in the cardia cause dysphagia; early satiety: feeling full after eating small amounts of food is highly indicative of an infiltrative disease, such as *Linitis Plastica* [48]. It may manifest as iron deficiency anemia due to occult bleeding or overtly as melena or hematemesis.

The presence of physical findings confirms M1 disease and directs treatment toward palliative care. Key signs include: lymphadenopathy: palpable Virchow's node (left supraclavicular) or Irish node (left axillary); peritoneal/abdominal metastases: Sister Mary Joseph node (umbilical), ascites, Blumer's raft (on rectal examination), and Krukenberg tumor (palpable ovarian masses); enlarged liver showing hepatic metastases. Paraneoplastic syndromes are rare systemic manifestations caused by the secretion of biologically active substances from the tumor, rather than by direct invasion [50]: acanthosis nigricans (hyperpigmented, velvety skin) and Leser-Trélat sign (sudden onset of multiple seborrheic keratoses) [48]; Trousseau's syndrome (migratory thrombophlebitis) and microangiopathic hemolytic anemia; polyarteritis nodosa and membranous nephropathy.

Upper gastrointestinal endoscopy *with biopsy:* upper gastrointestinal endoscopy is the gold standard for diagnosis. It is essential to take multiple biopsies (at least seven) from suspicious lesions to achieve a diagnostic sensitivity approaching 98-99% [51]. The use of modern techniques, such as chromoendoscopy and narrow-band imaging (NBI) endoscopy, helps to detect subtle early lesions [52]. **Endoscopic ultrasound (EUS):** endoscopic ultrasound (EUS) is a high-resolution method for local T and N staging. This information is critical for determining resectability and planning neoadjuvant therapy [7]. **Computed tomography (CT) and PET-CT:** contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis is the standard imaging method for evaluating distant metastases [8]. It is important to note that both CT and PET-CT often fail to detect small-volume peritoneal disease [53, 54]. **Staging laparoscopy with peritoneal cytology:** staging laparoscopy (SL) plays an essential role in patients with locally advanced (cT3/T4) or diffuse tumors who have no obvious metastases on imaging studies [55, 56]. SL can identify radiologically occult peritoneal metastases in 20-30% of these patients [34]. Positive Peritoneal Cytology, CY1 determines M1 status and excludes the possibility of radical surgical treatment. [56].

Tumor markers: serum tumor markers, such as Carcinoembryonic Antigen (CEA), CA 19-9, and CA 72-4, are commonly used [57-58]. They are useful for monitoring recurrence after treatment if they were elevated at baseline [17, 55]. Combined testing of the three markers has higher sensitivity and specificity compared to each marker individually [57].

Surgical treatment (R0 resection) is the central component of multimodal therapy for resectable gastric cancer, which means microscopically clear resection margins. This is a prerequisite for any chance of long-term cure [60]. Lymph node dissection is classified as D1 (perigastric) and D2 (extended, including extraperigastric lymph nodes). The historical debate over D1 versus D2 has been intense; early Western studies showed high morbidity and mortality with D2 dissection in non-specialized centers, often due to the routine inclusion of splenectomy and pancreatectomy. Today, however, D2 lymphadenectomy is the standard of care when performed by experienced surgeons in high-volume, specialized centers [61].

The main types of resection are determined by the location of the tumor: distal/subtotal gastrectomy for tumors in the distal part of the stomach; total gastrec-

tomy for tumors in the middle or proximal part of the stomach; and proximal gastrectomy as an option for some proximal tumors.

Reconstruction of the digestive tract after gastrectomy is key to the patient's quality of life. After distal gastrectomy, options include Billroth I/II and Roux-en-Y anastomoses [62]. Roux-en-Y reconstruction is the preferred method, as data show that it significantly reduces long-term complications, such as bile reflux and reflux esophagitis, thereby improving the quality of life compared to Billroth II [63]. After total gastrectomy, the standard reconstruction is Roux-en-Y esophagojejunostomy.

Gastrectomy is associated with significant long-term morbidity. There are two main groups of consequences: **1. Post-gastrectomy syndromes:** common complications are dumping syndrome (rapid passage of hyperosmolar chyme), fat malabsorption, and gastroparesis, which contribute to weight loss [64]; **2. Nutritional deficiencies:** patients require lifelong monitoring and supplementation due to vitamin B12 deficiency (due to loss of intrinsic factor), iron malabsorption, and subsequent risk of anemia and metabolic bone disease [64, 65].

For patients with metastatic (stage IV) or unresectable locally advanced gastric cancer, the goal of treatment is symptom palliation, prolongation of survival, and maintenance of the quality of life. This includes performing a gastrojejunostomy for distal obstruction or, in rare cases, to control life-threatening bleeding [66]. The REGATTA study shows that there is no survival benefit from non-curative gastrectomy in M1 disease [67]. Endoscopic interventions offer alternatives to surgery with low morbidity. The placement of self-expanding metal stents (SEMS) is an established method for relieving malignant obstruction of the gastric outlet, often providing a better quality of life compared to surgical bypass [66, 68], while ablative techniques can be used to control localized bleeding.

Modern palliative systemic therapy is guided by biomarkers, requiring molecular testing for HER2, MSI status, and PD-L1 expression to guide treatment. The main classes of agents used include: **chemotherapy**: dual therapy with platinum and fluoropyrimidines is the standard first-line treatment; **targeted therapy**: trastuzumab for HER2-positive cancer is a key example [46, 69]; **immunotherapy**: immune checkpoint inhibitors are used in tumors with high microsatellite instability (MSI-high) or PD-L1-positive tumors [70]. Advanced age alone should not be a contraindication for targeted and biological therapies [71]. Radiotherapy is used to achieve local palliative goals, such as controlling uncontrollable bleeding from the primary tumor or relieving pain from bone metastases [66]. Specialized management of pain and nausea is also essential. Nutritional support is mandatory to alleviate cachexia, and enteral feeding should be initiated if oral intake is compromised [68].

DISCUSSION

The prognosis for gastric cancer is generally poor, mainly due to late diagnosis. Understanding key prognostic factors, stage-specific survival, and principles of follow-up after treatment is essential for patient management. Several factors have a strong influence on survival: **1. Pathological stage (TNM)**: TNM stage is the most dominant prognostic factor [60]. **2. R status**: achieving R0 resection (microscopically negative margins) is essential for cure. **3. Lymph node involvement**: a high number of positive lymph nodes (N3a/N3b) is associated with a significantly worse prognosis. **4. Histological and molecular subtype**: diffuse histology and the genomically stable (GS) molecular subtype usually carry a worse prognosis, while the MSI subtype has a relatively favorable prognosis. **5. Peritoneal involvement**: positive peritoneal cytology (CY1) or macroscopic peritoneal metastases are powerful independent indicators of a very poor prognosis, with median survival measured in months [23, 56].

Approximate 5-year net survival data based on data from England illustrate the strong influence of stage at diagnosis: Stage 1: approximately 65%. Stage 2: approximately 35%. Stage 3: Approximately 25%. Stage 4 (M1): 5-year survival is extremely rare (0-5%); 1-year survival is approximately 20% [27]. The median survival for peritoneal disease is only 200-400 days.

The goals of follow-up after treatment are early detection of recurrence and management of the long-term effects of surgery. Clinical and imaging follow-up – regular clinical examinations are necessary, combined with serial CT scans (chest/abdomen/pelvis), usually every 6 months for the first 2-3 years, then annually; endoscopic follow-up – repeat endoscopy is necessary to monitor the gastric remnant or anastomosis for recurrence, especially after subtotal gastrectomy; tumor marker monitoring: serial measurement of CEA, CA19-9, and CA72-4, if elevated before treatment, may serve for early detection of recurrence; nutritional monitoring: there is a critical need for long-term nutritional monitoring and supplementation to manage the consequences of gastrectomy [14, 64, 65].

Conflict of interest: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

Ethical statements: *The authors declare that no clinical trials were used in the present study.*

The authors declare that no experiments on humans or human tissues were performed for the present study.

The authors declare that no informed consent was obtained from humans, the donors or donors' representatives participating in the study.

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