

Gastric Cancer: A Brief Review, from Risk Factors to Treatment

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Abstract

Gastric cancer (GC) is a globally relevant disease. It is the fifth most common neoplasm and the third most lethal in the world, being associated with more than 780,000 deaths in 2018. Developed countries tend to have a higher GC incidence, especially those located in Asia. GC development is associated with modifiable and non-modifiable risk factors, including *Helicobacter pylori* infection, unhealthy eating and lifestyle habits, advanced age, male gender, and low socioeconomic status. GC prevention involves *H. pylori* eradication, elimination of bad habits, and the use of screening methods. The classification systems for GC developed by the World Health Organization, Lauren, and Ming are the most used for GC staging and take into consideration the anatomical and histological characteristics. Furthermore, the recent characterization of the GC molecular profile has led to the proposal of new classification subgroups. The symptoms of GC are not pathognomonic and can include loss of appetite and weight, anemia, abdominal pain, early satiety, gastrointestinal bleedings, constipation, diarrhea, indigestion, vomiting, pyrosis, dysphagia, swelling of supraclavicular lymph nodes, and nodules in epigastric and umbilical regions. The diagnosis of GC is carried out through clinical evaluation followed by upper gastrointestinal endoscopy and biopsy. Computed tomography and endoscopic ultrasound are important diagnostic methods for the assessment of the disease. Moreover, the use of tumor markers as a diagnostic technique might be a possibility; however, more studies are needed to evaluate its accuracy. There is no universally recommended standard for the treatment of GC. Surgery is considered a potentially curative method. However, the association with a multimodal approach, such as chemotherapy and chemoradiotherapy, is strategic for improving survival.

Keywords: Gastric cancer, Epidemiology, Diagnosis, Classification, Treatment

Introduction

Gastric cancer (GC), also known as stomach cancer, is a worldwide health problem. Anatomically, it can occur from the gastroesophageal junction to distal portions of the stomach [1,2]. Considering both sexes, worldwide, it is the 5th most common neoplasm (5.7%) and the 3rd cause of mortality among malignancies, leading to approximately 782,000 deaths in 2018 [3]. The incidence varies geographically but 50% of new cases are diagnosed in developed countries. High incidence is observed in Asia, Latin America, and in the central and eastern parts of Europe [4]. There are several ways to classify GC, but the most used is Lauren's Classification, which proposes two main histological groups: intestinal and diffuse. This classification is important because there are marked etiological, pathological, and epidemiological differences

between the subgroups, guiding the clinical approach for each patient [5,6]. Despite the high worldwide incidence, several studies are beginning to show a gradual reduction in the number of new cases associated with factors including *Helicobacter pylori* eradication, increased access and better storage of fresh foods, and changes in diet and lifestyle (increased physical activity and reduced sodium intake, alcohol consumption, and smoking) [7-9]. In this mini-review, the risk factors, ways to prevent, and possible classifications for GC as well as the clinical manifestations, diagnostic methods, and the main treatments for this malignancy will be addressed.

Risk Factors

GC is a multifactorial disease associated with modifiable and non-modifiable risk factors. The infection by *H. pylori*

is the major risk factor for GC [10]. From the beginning of the infection, the carcinogenesis process usually takes 20-30 years to occur [11]. Moreover, acquiring *H. pylori* during childhood is a risk factor as well [12]. Furthermore, *H. pylori* virulence factors like *cagA* and *vacA* also increase GC risk [13]. Other modifiable risk factors include smoking, high alcohol consumption, obesity, and eating salty foods as well as red, smoked, and processed meat, besides the low ingestion of fresh fruits and vegetables [14].

Non-modifiable factors for GC development include genetic aspects such as E-cadherin mutation, IL-1, and CYP19A1 polymorphisms, hereditary diffuse gastric cancer (HDGC), and familial adenomatous polyposis (FAP). Furthermore, other hereditary conditions may increase the GC risk, like cancer history in first-grade relatives [15]. Intestinal metaplasia, autoimmune gastritis, and pernicious anemia are also risk factors for GC [16,17]. Older age, male gender, A+ blood type, history of gastric surgery, and low socioeconomic conditions increase the risk of gastric carcinogenesis as well [18]. Regarding ethnicity, Afro-Americans, Hispanics, and American Indians have a higher risk of cardia GC, while non-cardia GC predominates in the white population [19].

Prevention

GC prevention involves primary and secondary prevention. Primary prevention includes dietary modification such as reduced salty food ingestion and increased fresh fruits and vegetable intake as well as avoiding smoking and high alcohol consumption [10]. *H. pylori* eradication and improvement of sanitary and hygienic conditions are other ways to prevent GC [20,21]. The use of screening methods, through endoscopy and photofluorography, for example, is the focus on secondary prevention to promote early detection and treatment [22]. *H. pylori* treatment may also reduce GC risk and decrease the death rate [23].

Anatomopathological Classifications

The main GC classification systems are those proposed by the World Health Organization (WHO), Lauren, and Ming [24].

According to the WHO, gastric adenocarcinoma is separated into subgroups that include papillary, tubular, mucinous, and mixed carcinoma. The poorly cohesive carcinoma type includes the signet ring cell carcinoma [26].

Lauren's classification is the most useful and widely applied in GC [27]. According to this system, most gastric cancers are adenocarcinomas and present two main histological types: intestinal and diffuse; besides the indeterminate type [25]. The intestinal type is originated

from chronic inflammation and progresses via a chronic gastritis-atrophy/metaplasia-dysplasia-carcinoma sequence [29], whereas the diffuse type is composed by separated single cells or small clusters of cells which diffusely infiltrate the layers of the gastric wall [24].

The Ming's classification separates GC into expansive and infiltrative types. The first grows in mass and by expansion, resulting in the tumor nodules, whereas, in infiltrative carcinoma, tumor cells invade the gastric wall individually [28].

Furthermore, based on the recent characterization of the GC molecular profile, four new subgroups have been proposed for the diagnosis and classification of the disease [30]. The Epstein-Barr virus-associated GC (EBVaGC) is one of those subgroups and results from the neoplastic infection caused by EBV that leads to clonal growth of infected epithelial cells as well as to atrophic gastritis [31]. Global hypermethylation of CpG island in EBVaGC induces epigenetic silencing of tumor suppressor genes and seems to be crucial for carcinogenesis [32]. Thus, considering that EBV infection is associated with about 10% of GC cases, serological screening for EBV-specific immunoglobulins was supposed to be useful in the identification of groups with a high GC risk. However, increased prevalence of EBV previous exposure and lack of more accurate markers are still a challenge for achieving that purpose [33,34]. The chromosomally unstable carcinomas represent another GC subgroup, and certain copy-number alterations are associated with specific histological types. While copy-number gains at 8q, 17q, and 20q are usually associated with the intestinal type, gains at 12q and 13q are commonly related to the diffuse type [35]. Microsatellite unstable tumors compose another subgroup characterized by elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins. Finally, the genomically stable tumors are associated with the diffuse histological variant and occasional mutations [36].

Symptoms

GC symptoms are often not pathognomonic, besides being often confused with the clinical presentations of other less severe pathologies, which contributes to late diagnosis, subsequent worsening of clinical condition, and poorer prognosis. Among the main clinical manifestations, stand out the loss of appetite and weight, early satiety, anemia (caused by the tumor-related bleedings), abdominal pain, nausea, and vomiting with blood or not. Moreover, indigestion, constipation or diarrhea, pyrosis, and dysphagia are often observed [37,38]. In advanced stages of the disease may occur the swelling of the epigastric region and supraclavicular lymph nodes as well as the appearance of nodules in the umbilical region [37].

Diagnosis

First of all, a detailed history must be obtained from the patient and physical examination must be thoroughly performed by physicians [39]. If GC is suspected, upper gastrointestinal endoscopy and biopsy are recommended, especially for analysis of the location and dissemination of potential gastric injuries [40].

The endoscopic findings of gastric cancer include polypoid or ulcerative injuries, spontaneous bleedings, the abnormal coloring of the affected region, and injuries similar to gastritis [41]. In addition, the endoscopy allows the analysis and classification of superficial tumors, which are subdivided into five types of injuries: (a) depressed lesions, that protrude into the tissue and have converging folds with abrupt cuts; (b) the flat lesions, which do not have projections, present a reddish color, and, sometimes, a whitish discoloration; (c) the elevated lesions, which are slightly protuberant, may present a redness or pallor coloring, and globular or lobular appearance [42]; (d) protruding lesions, which correspond to polypoid tumors; and (e) excavated superficial tumors, which invade more deeply the tissues [43].

The computed tomography is useful for accurately evaluating the tumor localization, possible metastasis, and small injuries in the mucosa, whereas the disease extension and injuries degree in the gastric wall can be assessed by endoscopic ultrasound. However, the latter technique is unusual, due to its higher costs and more invasive characteristics [44].

The serum quantification of tumor markers such as CA 72-4 may be utilized as a laboratory diagnostic tool [45]. These molecules may be found at altered levels in blood, tissues or other biological liquids, indicating the appearance of neoplastic cells or cancer [46]. Some studies demonstrated a relationship between alterations in the CA 72-4 concentrations and advanced degrees of the disease. However, further studies are needed in order to better evaluate the accuracy of this technique [45].

Moreover, it is valid to consider that population-based screening methods may support the diagnosis and treatment process. In some Asian countries, where there is a higher incidence of gastric cancer, the adoption of strict screening programs favored early detection and increased the chances of curative interventions [47]. A Korean study showed a reduction in GC-specific mortality and a higher survival rate in groups screened by gastroduodenal endoscopy [48]. Despite this approach may not be cost-effective for countries with low GC incidence, specific screening programs are suggested for high-risk groups [49,50].

After all, when diagnosed, GC must be staged, allowing the choice of the proper therapeutic approaches. Currently, the most widely used protocols for GC staging and TNM classification are respectively signed by the American Joint Committee on Cancer and International Union Against Cancer (UICC) [51,52].

Treatment

The prognosis and treatment of GC consider factors such as the location and staging of the tumor, the number of lymph nodes affected, and the presence of metastasis [40]. There is no general standard for adjuvant therapy around the world; however, phase III trials regionally conducted have been guiding local standards [53]. The treatment should be discussed by a multidisciplinary team, comparing risk and benefit factors [54].

The European Society for Medical Oncology Guideline suggests endoscopic resection for initial gastric cancer if it is in association with the mucosa, well-differentiated, ≤ 2 cm, and without ulcers. Laparoscopic surgery has also been recommended for early gastric cancer, despite uncertainties regarding effectiveness in situations that require D2 lymphadenectomy compared with open surgery. For tumors in IB-III stage, total or subtotal gastrectomy is indicated in association with perioperative therapy [55].

Surgery is considered the only potentially curative management for localized GC, but since it is associated with low survival when used alone, the multimodal management becomes more strategic [56]. The MAGIC study could support this notion when evaluated the perioperative chemotherapy approach associated with surgery and isolated surgery. Comparatively, patients treated with perioperative chemotherapy had higher overall survival (OS) [57]. The CRITICS study also compared the treatment of perioperative chemotherapy and preoperative chemotherapy with postoperative chemoradiotherapy. The first group had a better OS than the chemoradiotherapy group [58].

Besides lymph node dissection (LND) and preferable minimally invasive surgery [49], in western countries, multimodal treatment for non-metastatic advanced gastric cancer (AGC) has included neoadjuvant chemotherapy (Europe) and postoperative chemoradiotherapy (USA), while adjuvant oral chemotherapy has shown greater benefits over surgery alone regarding overall survival in Asian people [59]. Reduced surgical trauma, postoperative complications, and hospitalization period are reported among laparoscopic gastrectomy advantages over open gastrectomy, but the latter remains the better option for obese patients [49,60]. Despite D2 lymphadenectomy has been more well-indicated over D1 in advanced non-

metastatic cases [61,62], its application out of high-volume centers is still limited, especially due to high morbidity and mortality risks associated with the extent of resection and lack of advanced and specific surgical skills [49].

The palliative management of unresectable locally advanced, recurrent, or metastatic disease must consider the performance status (PS), comorbidities, organ function, and toxicity factors of the patient [55,63]. The most widely used scales for PS measurement are ECOG Performance Status [64] and the Karnofsky Performance Status [65]. Patients with better PS scores ranging up to 2 or at least 60, respectively, are the most indicated for receiving systemic therapy or to participate in clinical trials with novel agents [63]. Some patients may benefit from this approach as conversion therapy and undergo surgery thereafter [8,66]. Trastuzumab must be added to first-line therapy for HER2-positive AGC or gastro-oesophageal junction cancer [67]. Best supportive care should be available all the time during treatment, but second-line therapy may yield greater OS for fit patients. Continuous assistance may allow appropriate physical and mental health care as well as early diagnosis of recurrence [55].

Conclusion

The management of GC has been improved during the past few years. However, treatment upgrades should optimize adjuvant therapy role, regimen, and timing, as well as refine the surgical techniques. Screening approaches might also be extended in order to reduce cancer incidence.

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