

# Gastric cancer: review of etiopathogenesis, diagnosis, management and new genetic developments

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**Abstract.** Gastric cancer (GC) is the one of the leading causes of cancer-related deaths in the world. Within the last decades, the epidemiology has changed and a steady decline in incidence rates is manifesting. This effect is highlighted by the eradication of *Helicobacter pylori* and the high standards of hygiene and nutrition. They form the primary prevention. Patients with higher risk of developing gastric cancer should be screened for early detection. Gastrectomy enhanced with lymphadenectomy still remains the most viable option in gastric cancer therapy. Often diagnosed at an advanced stage, prognosis is usually poor with a median overall survival of less than twelve months. This review highlights the most important characteristics of this type of cancer, among which are mentioned the epidemiology, the risk factors, the genetics implications, the classifications, the diagnosis, the prevention and the treatment for early and advanced gastric cancer.

**Key Words:** gastric cancer, pathogenesis, therapy, premalignant lesions .

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## Introduction

The term gastric cancer (GC) is usually used for the carcinomas that are malignant tumors of the gastric wall with epithelial origins. A combination of environmental factors and alterations of specific genes can lead to this type of cancer. Based on histological features, Lauren classification system classifies GC into differentiated intestinal carcinomas and undifferentiated diffuse carcinomas. Early detection of both types is essential for the proper measures and the mass screening for it is expensive, and therefore is recommended only in regions with high incidence, such as East Asia, and senseless in low-incidence regions, such as Nord America (Sitarz et al 2018).

## Incidence and epidemiology

GC ranks 4th in the world for cancer, and the 2nd place for cancer mortality. The incidence and mortality though gastric cancer started to decline and was more significant in the developed countries of the world. The standardized mortality rate has declined in the world by 10-20% over the last decade. The tendency to decrease has affected only the intestinal type, because the incidence of infection with *Helicobacter pylori* was

significantly reduced. In contrast to the intestinal type, the incidence of diffuse gastric cancers has increased (Valean 2011). The incidence of GC has a different geographical spread. There are some areas with a higher risk and other with a lower risk of developing this disease. The high-risk areas include East Asia (China and Japan), Eastern Europe, and Central and South America, as opposed to Southern Asia and East Africa, Nord America, Australia and New Zealand which present a much lower occurrence rate (Kaneko and Yoshimura, 2001).

Distal GC represents 80% of gastric cancers, usually intestinal, with the most frequent occurrences in the developed countries, in persons with low socioeconomic status. The male to female ration is 2/1 and it's increasing with age.

Intestinal gastric cancer dominates the high-risk areas, with risk factors including old age, male, and black race. Diffuse gastric cancer has a uniform geographic inclination, occurring at younger ages, and equally affecting both sexes (Valean, 2011). A Japanese analysis (Kaneko and Yoshimura, 2001) highlights a declining incidence of the disease, but it's particularly to the young patients with noncardial, sporadic, intestinal type. On the other hand, an American study, based on the race and the age subpopulations highlights an increasing tendency of gastric neoplastic gastric lesions (Cisco et al 2008).

## Classification

According to the World Health Organization guidelines, gastric cancer is classified adenocarcinomas, signet ring-cell carcinomas and undifferentiated carcinomas (Sitarz et al 2018). Lauren Classification distinguishes two major subtypes of GC, intestinal and diffuse types, that contains microscopic and macroscopic differences.

Intestinal gastric cancer has the highest prevalence in the general population. It occurs sporadically and is related to environmental and dietary factors (salted fish and meat, cigarette smoking, smoked foods and alcohol consumption). Its structure comprises components of glandular, solid or intestinal architecture and also tubular structures (Lynch et al 2005).

The diffuse type happens in younger patients and occurs in families and it's called hereditary diffuse gastric cancer (HDGC). Its structure is characteristic by poorly cohesive clusters of cells which infiltrates the gastric wall, widespread thickening and rigidity, known as linitis plastica (Hansford et al 2015).

Other classifications are: Sporadic gastric cancer (SGCs), Early onset gastric cancer (EOGC), Gastric stump cancer (GSC) and Hereditary diffuse gastric cancer (HDGC) (Sitarz et al 2018).

Early onset gastric cancer is often multifocal or diffuse and more frequently observed in females. Sporadic gastric cancer occurs at the age 60-80 years, and males are more affected than females, especially in high-risk countries. SGC is defined as a carcinoma that occurs in the gastric remnant at least 5 years after the surgery for peptic ulcer.

Most cases of GCs appear sporadically, but in 5-10% family clustering (1-3% of all GCs) are inherited by the autosomal dominant mutation of CDH1 (La Vecchia et al 1992).

Molecular classification made by The Cancer Genome Atlas (TCGA) project and classifies GC in four molecularly unique subtypes: Epstein Barr virus (EBV) positive tumors, microsatellite unstable tumors (MSI), genomically stable tumors and chromosomal unstable tumors (Comprehensive molecular characterization of gastric adenocarcinoma., 2014).

## Premalignant lesions of the stomach

Endoscopy is the best screening method for this type of gastric cancer and it is only recommended in regions with high incidence, such as East Asia and it is considered senseless in low incidence regions, such as North America (Kaneko and Yoshimura, 2001). Additionally, endoscopic surveillance should be performed annually for patients considered to have high-risk factors: BRCA 2 mutations, hereditary nonpolyposis colon cancer syndrome, Peutz-Jeghers syndrome, Menetrier disease, polyp gastric and previous gastric surgery (Valean, 2011)

Adenomatous gastric polyp is a very rare disease, that represents only 10% of polyposis injuries. It's considered a premalignant lesion as it needs polypectomy when it's found and the patients need to be kept under surveillance for relapse. It has a malignancy risk when there are multiple lesions, the syndrome being called Peutz-Jeghers polyposis (Valean, 2011).

Dysplasia can evolve to cancer when the degree of severity is increased; when it's severe enough, dysplasia can turn into cancer in up to 75% of the cases within 2 years (Rugge et al 2000). Atrophic gastritis and intestinal metaplasia can evolve in GC through a process that begins with small lesions like atrophic

gastritis, then intestinal metaplasia, dysplasia and eventually GC, when the patients are exposed to different risk factors, such as infections, toxics or genetics. It is also shown that atrophic gastritis from Biermer anemia has a risk almost 3 times larger than non-Biermer gastritis (Rugge et al 2000).

Peptic ulcer surgeries on the stomach can sometimes lead to preneoplastic lesions. The risk is increased up to 4 times if the surgery is for gastric ulcer, and if the patient has Menetrier gastropathy the risk also increases by 15% (Koh and Wang, 2002). Obesity and gastroesophageal reflux disease can increase the risk 2-3% more, directly proportional to its degree (Crew and Neugut, 2006; Valean, 2011).

Another major risk factor is *Helicobacter pylori* infection. It is classified in a group 1 or definite carcinogen. In the general population, *H. pylori* infection reaches almost 60%, but it is more common in about 84% of GC. The correlation between the infection and injuries starts in a younger age (<40 years) and it's involved in both intestinal and diffuse types of carcinomas (Parsonnet et al 1991; Sitarz et al 2018). There is a consensus across the research as to the treatment. There are 2 main lines of treatment, the first line of treatment includes amoxicillin and clarithromycin or metronidazole, and if it doesn't succeed then the proposed second line treatment is bismuth salts, a proton pump inhibitor, tetracycline and metronidazole (Malfertheiner et al 2007). An interesting aspect of *Helicobacter pylori* infections happens in Africa, where, even though a large percent of the population is infected with *Helicobacter pylori*, GC is rare. One of the proposed theories that could explain this phenomenon, also called "the African Enigma" is a concomitant helminth infection (*Heligiosomoides polygyrus*) (Holcombe, 1992; Thyte et al 2003).

Infection with Epstein-Barr plays a role in GC development of carcinogenesis. The infection varies between different regions, being as low as 4% in China, or as high as 12.5% in Poland and up to 17.9% in Germany. EBV in carcinoma biopsies indicates that the tumor formation has been caused by the proliferation of a single infected cell (Sitarz et al 2018)

In the year 1998, mutation of the gene CDH1 was found in New Zealand, in three Maori families that were predisposed to diffuse gastric cancer. This type of gastric cancer is inherited and can affect individuals at a young age. The specific characteristic, the inactivating mutations of the Cadherin gene, has been identified in 30-50% of patients (Cisco et al 2008).

A study found that the expression of CDX2 in adenocarcinomas was positive in most digestive tract cancers (being as high as 95-100% in colonic CA and duodenal adenomas/CA), with occurrence being up to 70% of GC, indicating that the CDX2 gene is well expressed in a significant percentage of adenocarcinomas related to the digestive tract (Werling et al 2003).

## Risk factors and prevention

Despite declining trend worldwide, prevention of GC must remain a priority. The primary prevention especially includes *H. Pylori* eradication therapies, a healthy change in diet but also screenings for early detection. Healthy dietary habits including a low-sodium diet, low meat intake, especially red/cured meat, maintaining a proper weight, avoiding alcohol drinking and smoking are associated with a decreased risk of GC (Buckland et al 2015).

Tobacco smoking has been linked with higher occurrences of GC in Japan, with up to 60% in male populations and 20% of female populations (Nishino et al 2006).

A healthy diet, rich in vitamin C, fresh fruits and dark greens, with a high antioxidant intake might help in the prevention of gastric cancer. Toxic behavior, like alcohol abuse can lead to gastric cardia cancers and exposure to radiation, N-nitroso compounds, dust and nitrogen oxides are linked to higher GC occurrences as well (Lagergren et al 2000).

Screening and surveillance of patients with gastric cancer in the family or premalignant lesions should have periodic and careful endoscopic surveillance in a gastroenterological center. Endoscopic supervision has a valuable role in guidance and therapeutic decisions, especially the malignant lesions detected endoscopically will be an indication for gastrectomy (Valean, 2011).

## HDGC endoscopy protocol

The patients with high-risk of malignancy should make annual endoscopies as the optimal time or frequency is not known precisely. To minimize the procedure risks (bleeding risk), it is recommended that patients stop anticoagulants (clopidogrel, warfarin) before the procedure (van der Post et al 2015).

The endoscopy includes a white light definition endoscope in a session of minimum 30 minutes, so that there is enough time to perform a carefully inspection of the gastric mucosa and to collect biopsies. A combination of mucolytics (N-acetylcysteine) and antifoaming agent (simethicone) together with sterile water must be used to wash the gastric mucosa before examination, which is done using the foot pedal. The macroscopic appearances and any visible lesions are recorded and copied in images or video for future reference (van der Post et al 2015). In gastroscopy biopsies of lesions are taken, and with the help of imaging techniques such as CT scans or endoscopic ultrasonographies, they can be used to visualize the gastric wall layers. Since *Helicobacter pylori* is the most important carcinogen, the patients should all be tested for the infection and treated.

To correctly diagnose GC, multiple biopsies of lesions are needed to highlight the tiny foci of signet ring cells and the pale areas. In most cases where the lesions are visible, an endoscopic resection is performed for a reliable histopathological result.

The pale areas are visible on examination by white light however narrow band imaging may make them easier to visualize. Virtual chromoendoscopy doesn't confer much more information than white light. (van der Post et al 2015).

## Gastrectomy

Patients with a pathogenic germline CDH1 mutation usually have a gastrectomy indication for gastric cancer prophylaxes (van der Post et al 2015). The optimal timing is highly individualized. This type of procedure has an extraordinary impact on life. The decision of gastrectomy must be well calculated, thought out and prepared.

The current advices of a decisional counselling with pros and cons should highlight that the gastrectomy is better to be done around the ages 20 and 30 (Blair et al 2006). After the age of 75, prophylactic gastrectomy should be carefully considered. Many patients have been found to have tumor T1 stage after

prophylactic gastrectomy because there may be a stagnant period when the tumor cells do not spread or progress. (Norton et al 2007).

The surgery includes a total gastrectomy with a Roux-en-Y reconstruction, with the anastomosis jejuna-jejunal distal below 50 cm from the anastomosis esophagogastric, as this reduces the biliary reflux (van der Post et al 2015).

Even if it's a lifesaving procedure, prophylactic gastrectomy at gastric cancer with known mutation of CDH1 has significant risks. The overall mortality is 2% to 4%. Patients must be aware of the morbidity on long terms that includes dumping, diarrhea, weight loss and eating problems (van der Post et al 2015).

If patients with genetic mutations (like CDH1) don't want to pursue prophylactic gastrectomy they should be under strict surveillance, that includes biannual chromoendoscopy with biopsies and endoscopies. The careful observation should begin at a younger age than the youngest family member diagnosed with GC, by at least 10 years (Cisco et al 2008).

## Treatment

A multidisciplinary team is needed to plan an appropriate treatment in different stages of GC. The team should include at least a pathologist, a surgeon, a gastroenterologist and a medical and radiation oncologist (see figure 1).

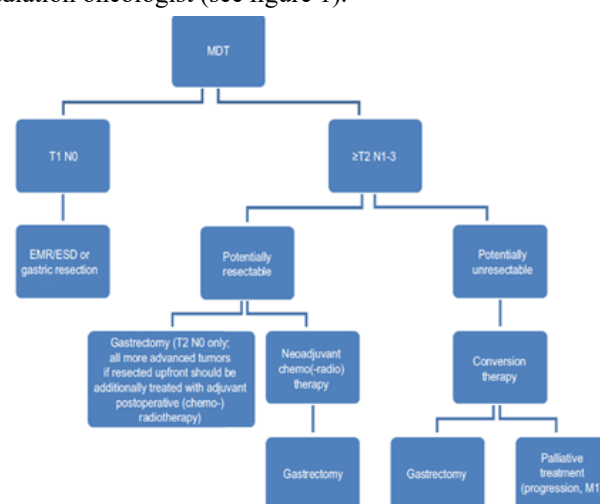


Figure 1. The seventh edition of TNM classification highlighted a new one according to the extent of gastric resection (Japanese gastric cancer association; Japanese gastric cancer treatment guidelines 2017).

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; MDT, multidisciplinary team.

In 1998, the Japanese Gastric Association standardized the regional lymphadenectomy based on the location of tumor and the respective regional node drainage. They were grouped as N1, N2, N3 and N4 and the procedures that depend on the range of lymphadenectomy were D1, D2, D3. The lymph node along the lesser curvature (station 1, 3 and 5) and the greater curvature (station 2, 4 and 6) form N1. Station 7 includes the nodes along the left gastric artery with the common hepatic artery (called station 8) and the celiac artery (called station 9) and the splenic artery (station 10 and 11) have been grouped as N2.

The lymph nodes along the middle colic artery (station 15) and lower paraesophageal lymph node and diaphragmatic lymph (station 16) are grouped as N4 (Kajitani, 1981; Ushijima and Sasako, 2004).

In the last years endoscopic mucosal resection has been implemented in early GC treatment (T1aN0M0) and in intraepithelial neoplasia, as it can provide the same effect as traditional surgery, and is often successfully. On the other hand, when the lesions are in advanced stage, the survival is less than 1 year (Jou and Rajdev, 2016).

## Chemotherapy

For patients with locally advanced and metastatic disease, chemotherapy remains the mainstay treatment. Chemotherapy with platinum, irinotecan, epirubicin, fluoropyrimidines and taxanes are some therapy options. In the last few years two drugs, trastuzumab and ramucirumab, new targeted agents, have been approved for metastatic gastric cancer (Jou and Rajdev, 2016). Chemotherapy offers a moderate survival advantage, but first of all is palliative.

When compared to single agents, combination therapy is associated with a higher response rate and increased survival, with the most commonly used combination being cisplatin and fluorouracil (CF) or with epirubicin.

Treatment options can be limited after the first-line of chemotherapy, most patients have a worsened performance status. The second line chemotherapy with irinotecan and taxanes or docetaxel demonstrated a survival advantage (Kang et al 2012; Thuss-Patience et al 2011). Despite all chemotherapy treatments the average survival is less than a year, so new treatment options are needed.

## Targeted therapies

### Human epidermal growth factor receptor 2 inhibitors (HER2)

HER2 represents a transmembrane tyrosine kinase receptor. This means that it's a part of the epidermal growth factor receptor family. Trastuzumab it's the first approved agent. He inhibits HER2 mediated signaling and its area of action is on extracellular domain of the human epidermal growth factor receptor 2. Added to standard chemotherapy, has a beneficial role in survival and response to treatment. (Bang et al 2010).

### EGFR inhibitors (HER1)

GC comes with overexpression of EGFR in the most cases, around 30-60% and goes with a poor prognosis. Cetuximab is a monoclonal IgG1 antibody that was added in chemotherapeutic plan but with this agent a higher rate of chemotherapy toxicity was observed (Jou and Rajdev, 2016).

### Vascular endothelial growth factor receptor inhibitors (VEGFR)

In 30-60% of gastric cancer patients, VEGFR factor can be overexpressed and is associated with a worse prognosis. Bevacizumab and Ramucirumab are some humanized monoclonal antibodies against VEGFR. Ramucirumab it's a part of the treatment plan for advanced gastric cancer administered alone or in combination with paclitaxel (Wilke et al 2014).

### mTOR inhibitors

mTOR, represents an intracellular key serine/threonine protein kinase that goes in regulate cell growth, motility and angiogenesis; Everolimus, an oral m TOR inhibitor, was used and evaluated in combination with paclitaxel as second line treatment for GC (Ohtsu et al 2013).

### c-MET inhibitors

c-MET is a tyrosine kinase receptor. Their amplification goes with an unfavorable evolution and a low survival rate. In evaluating Rilotumumab in combination with ECX, in pathologies like advanced gastroesophageal cancer highlights that a high c-MET expression can have clinical benefits (Iveson et al 2014).

### Poly ADP-ribose polymerase inhibitors

Poly ADP ribose polymerase inhibitors (PARP) are forming a family of proteins, that are involved in tumor cell death and their repair mechanism.

Studied in a second line phase II trial for metastatic or recurrent gastric cancer, Olaparib (the representative drug), in combination with paclitaxel was compared with paclitaxel monotherapy. The results were that treatment with PARP and paclitaxel is associated with the death of tumor cells more than paclitaxel monotherapy (Rouleau et al 2010).

Chemotherapy can be used in patients with good performance status (PS 0-1). In Europe there are three cycles of chemotherapy before surgery and three cycles after surgery. The most common used protocols are:

- ECF-which includes epirubicin, cisplatin and 5 FU,
- ECX which includes epirubicin, cisplatin and capecitabine,
- EOF includes epirubicin, oxaliplatin and 5 FU

and EOX includes epirubicin, oxaliplatin and capecitabine. Second line therapy is based on irinotecan, docetaxel and paclitaxel (Dank et al 2008). In the case of late disease progression after first line therapy, guides indicate to retry the same treatment schemes again (Waddell et al 2014). High occurrence of relapses is still observed. In patients that are in advanced stages, radio-chemotherapy is highly recommended. Cases of advanced GC with anemia or with pyloric or cardiac obstruction, have radiotherapy indication. The doses used of 30 Gy divided in 10 fractions can diminish bleedings and can improve the food passage, but only for 3-6 months (Tey et al 2007).

Trastuzumab is used for patients with inoperable GC, as a palliative drug and it's considered the standard treatment for HER2 positive carcinomas. It can also be used in combination with another drug, like capecitabine or 5FU and cisplatin.

Second line chemotherapies are based on docetaxel, paclitaxel, also called taxane. Others like irinotecan or ramucirumab are used like a single agent or in combinations. Their combination involves paclitaxel. Ramucirumab can be added to paclitaxel and compared with paclitaxel alone, yields in better survival rates for the combination (Wilke et al 2014).

## Immunotherapy

The immune system is involved in protection of our bodies against external and internal factors, this includes tumor cells protection. It's done with the help of immune checkpoints proteins, which have generated an increased interest in GC treatment. There are two antibodies, ipilimumab and tremelimumab,

that are evaluated in advanced cancers and are fully humanized CTLA44 (Hodi et al 2010; Ralph et al 2010).

## Nutrition and postsurgical care

The mental impact of a surgery is difficult, but a gastrectomy has a psychological, physiological and metabolic impact that should not be underestimated. Global quality of life scores recover are around 12 months post operation. Symptoms like abdominal pain, problems with eating and absorbing nutrients persist a long time after surgery (Worster et al 2014).

The patients that went under gastrectomy should be educated about making changes in their style of living. Initially patients should have small and fractional meals otherwise they may appear abdominal pain. Early and late dumping syndrome can happen as a result of gastrectomy. The difference between them is that in early dumping the food enters the small intestine directly at an early stage of digestion and in late dumping are the insulin changes in a very short time, due to faster digestion. Healthy dietary changes can improve the symptoms of dumping syndrome. Other problems like steatorrhea, lactose intolerance, dysphagia, modification in medication absorption or alcohol, minerals and vitamins malabsorption, or osteoporosis with osteopenia and osteomalacia require a proper treatment with supplements. Changes in health like extreme fatigue, hair loss, prolonged changes need to be properly supervised and treated. Before and after surgery, patients with gastric cancer should consult a dietician for the management of postsurgical indications. The recovery after surgery is unique for every patient; there are no rules. Patients have different recovery rates, from the nutritional part of intolerances to the complications of the gastrectomy. The most notable changes will happen within the first year and careful medical observation must be practiced.

## Future research on gastric surveillance

In the future, considering the rarity of this condition, GC needs to be evaluated and treated in multicenter studies with strictly defined protocols and investigations. In light of emerging endoscopic technologies, such as narrow band imaging, blue laser imaging, I scan, autofluorescence imaging, IHB-enhancement and confocal endomicroscopy, more research is required to further study the optimal methods for monitoring of individuals with risk of GC (van der Post et al 2015).

Furthermore, a multiple biopsy protocol leads to scarring that can masquerade as pale areas (where tumor cells of diffuse gastric cancer are). An endoscopic atlas created by endoscopists performing regular endoscopies on CDH1 mutation carriers would be very useful to help standardize protocols and improve lesion recognition earlier (van der Post et al 2015).

The pathology of gastric cancer is difficult to recognize and by its unique way. This should involve experience in the pathology and determination to get it done properly from diagnosis to treatment. A gastrectomy team must be involved and it is needed to provide a high-quality and accurate diagnosis in biopsies and also in resection specimens. Building a virtual bank with premalignant lesions, malignant lesions all kind of them that have been observed in gastric cancer pathology would be useful even further in providing timelier and more accurate diagnosis.

To understand the biology, the phenotype of cancer and the specimens of CDH1 mutation carriers it's vital to examine the full gastrectomy (van der Post et al 2015). The paraffin block from the gastrectomy piece can be sent to a histopathology laboratory to complete the result with immunohistochemistry techniques (van der Post et al 2015).

One of the most important things in future research on gastric surveillance are the premalignant lesions. New studies are trying to highlight them as quickly as possible and treat them to prevent their evolution into gastric cancer.

The mutation of CDH1 is directly involved in pathogenicity of malignant gastric lesions and it's imparted through  $\alpha$ -catenin-associated pathways (Hansford et al 2015) and will represent a key point for future research.

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