

Stomach Cancer (Gastric Cancer) — Classification and Prognosis

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Over the past several years, more and more individuals attract malignant gastric cancer. In many cases, however, the initial symptoms of the disease are so non-specific that the tumor is not diagnosed until it is in an advanced stage, resulting in the prognosis being worse. Which risk factors promote the development of gastric cancer, and what are the treatment options once the diagnosis of gastric carcinoma has been made? In the following article, you will find out everything you need to know about gastric cancer.



Definition of Gastric Cancer

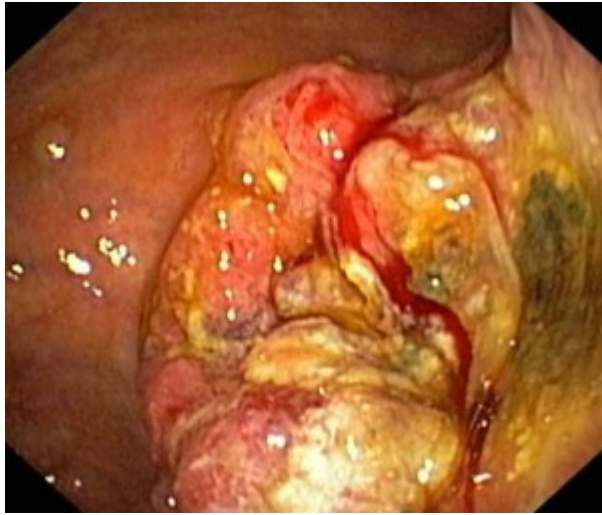
Gastric cancer refers to the formation of malignant neoplasms of the stomach lining (ICD code C16).

Epidemiology of Gastric Cancer

Gastric cancer has wide geographical variations. Previously, it was one of the most common cancers in Western Europe and the United States, but the incidence has currently declined. It is still common in countries such as China and Japan.

Worldwide, gastric cancer is still the **second most common cancer** of the [gastrointestinal tract](#). It is also the **third most common** cause of **cancer-related deaths** in the world, estimating about 723,000 deaths worldwide.

Men are slightly more affected than women, with the peak incidence age being **over 50 years**. Gastric cancer usually has an unfavorable prognosis because it is often diagnosed late when metastasis has already occurred due to the initial vague, nonspecific symptoms.



[Image](#): "Stomach Cancer in Advanced Stage" by Robert Weemeyer. License: [Public Domain](#)

Etiology of Gastric Cancer

Factors that promote the development of gastric cancer

Multiple factors have been found that are linked to the development of gastric cancer. The biggest risk factor, however, is gastritis caused by ***Helicobacter pylori***, followed by **type A gastritis**. A *Helicobacter pylori* infection increases the risk for gastric carcinoma by 4–6 times.

Gastric cancer is linked with the consumption of certain foods, especially foods rich in nitrate, whereas foods rich in fiber and antioxidants are thought to protect the stomach. Smoking also increases the risk of gastric cancer. Furthermore, partial gastrectomy, the presence of certain gastric adenomatous polyps, and giant fold gastritis pose a certain risk for gastric cancer.

The following diseases pose a risk for gastric cancer:

- [Peutz-Jeghers syndrome](#)
- FAP = [familial adenomatous polyposis](#)
- Li-Fraumeni syndrome
- Mutations in the CDH1 gene
- [HNPCC](#) (hereditary non-polyposis colorectal carcinoma)

Signs and Symptoms of Gastric Cancer

Gastric cancer often remains undiagnosed for a long time due to the vague non-specific initial symptoms, such as abdominal discomfort, indigestion, nausea, heartburn, bloating, decreased appetite, night sweats, fatigue and weight loss. A sudden aversion to meat may be an indicator of gastric cancer. In many cases, however, the complications of the tumor, such as pyloric stenosis and bleeding, are the first significant symptoms of the disease.

On clinical examination, sometimes the left supraclavicular lymph node is palpable (the **Virchow's lymph node**) which may hint to the underlying gastric cancer. Hepatomegaly and ascites may occur in advanced stages. In cases of aggressive, metastasizing

growth, **malignant acanthosis nigricans**, or cutaneous paraneoplastic syndrome, may occur.

Diagnosis and Clinical Signs of Gastric Cancer

The following studies are available for diagnosing and staging gastric cancer:

- Esophagogastroduodenoscopy with multiple biopsies
- X-rays with contrast agents
- Abdominal sonography
- Endosonography
- Abdominal/chest/Pelvic CT scan with contrast
- Skeletal scintigraphy
- Positron emission tomography (PET)
- *HER2-neu* testing in cases of documented or suspected metastatic adenocarcinoma

The tumor markers CA 19-9, CA 72-4 and CEA are relevant for monitoring the progression of the tumor and the treatment response.

Most histological examinations will often reveal adenocarcinoma (90%), including the **signet-ring cell carcinoma**. Signet-ring cell carcinoma is an adenocarcinoma, whose cells produce large amounts of mucus pushing the nucleus against the cell membrane, morphologically resulting in the typical signet ring appearance. Signet-ring cell carcinomas have a rather negative prognosis. Squamous cell carcinoma, gelatiniform cancer, small cell carcinoma, and undifferentiated carcinoma are rarer forms of gastric cancer.

Location and spread of gastric cancer

Gastric cancer is most commonly located in the antrum and pylorus, followed by the lesser curvature and cardia.

Note: This tumor metastasizes early!



[Image](#): "Bone Metastases in Gastric Carcinoma" by Hellerhoff.
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How gastric cancer spreads:

- Infiltrates the gastric wall and the peritoneum
- Local invasion, per continuitatem, into the esophagus, duodenum, colon, and pancreas
- Lymphogenous metastasis to lymph nodes along the lesser and greater curvature, the celiac artery, the para-aortic and mesenteric lymph nodes
- Metastases in ovaries (Krukenberg tumor) or in the pouch of Douglas
- Hematogenous spread to the liver, lungs, bones, and brain

Note: 30% of affected individuals with stage pT1b cancer have lymph node metastases!

Classification of Gastric Cancer

The classification systems for gastric carcinoma

The so-called **Lauren's classification** groups gastric cancers according to their histological growth pattern into two main types:

- **Intestinal type:** These are well-differentiated, slow growing and gland forming cancers. They have a more favorable prognosis.
- **Diffuse type:** These are poorly-differentiating, fast-growing (aggressive) and do not form glands but scatter throughout the stomach, possibly penetrating surrounding organs. They have a rather negative prognosis due to its tendency to quickly metastasize to the lymph nodes.
- **Mixed type:** These gastric cancers have both types - intestinal and diffuse - simultaneously.

In some gastric cancers (5%), the stomach becomes rigid, thickened and leather-like, called **linitis plastica**. It is due to extensive infiltration by the malignant cells. These patients have an extremely poor prognosis.

Image: "Ulcerating Gastric Carcinoma" by Kuebi. License: [CC BY-SA 2.0](https://creativecommons.org/licenses/by-sa/2.0/)



Borrmann classification divides the advanced gastric cancer into four types on the basis of their **macroscopic** (gross) appearance:

- Type I: Polypoid growth
- Type II: Fungating growth
- Type III: Ulcerating growth
- Type IV: Diffusely infiltrating growth

Classification based on **location**:

- Approximately 70% of tumors are located in the antrum.

Note: The frequency of distal gastric cancer has declined, which is attributed to implementing eradication therapy for *Helicobacter pylori* infections.

- lesser curvature
- cardia
- tumors of the gastroesophageal junction

Note: Cancer of the gastroesophageal junction has become more and more frequent! For the past several years, the incidence of gastroesophageal cancer has sharply risen! Even after stage T0 resection and broad application of lymph node dissection, the recurrence rate is high with this specific tumor location.

The **Siewert classification** for adenocarcinoma of the gastroesophageal junction (AEG) is as follows:

- AEG I: true carcinoma of the distal esophagus ([Barrett's esophagus](#), associated with reflux)
- AEG II: true carcinoma of the cardia
- AEG III: subcardial gastric carcinoma

Grading

Histologically, the degree of differentiation (**grading**) of the tumor is determined from G1 to G4. The G1 being well-differentiated, slow growing with a good prognosis; and G4 being undifferentiated, aggressive, with poor prognosis.

Staging

The **staging**, using the TNM classification system, takes place in order to assess the extent of the disease, as well as to plan the therapeutic intervention. The following TNM classification system is used for staging gastric carcinoma, according to the 2010 American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*.

T = Primary tumor according to the depth of infiltration

- TX - primary tumor (T) cannot be assessed
- T0 - no evidence of primary tumor
- Tis - carcinoma in situ
- T1 - the tumor invades the submucosa
- T2 - the tumor invades the muscularis propria
- T3 - the tumor invades the serosa
- T4 - the tumor perforates the serosa, surrounding structures are affected

N = regional lymph node involvement according to the number of lymph nodes affected

- N0 - no regional lymph node metastases
- N1 - 1 - 2 regional lymph node metastases
- N2 - 3 - 6 regional lymph node metastases
- N3 - more than 7 regional lymph node metastases

M = formation of distant metastases

- M0 - no distant metastases
- M1 - confirmed distant metastases

Residual Tumor (R)

Following surgery, the residual tumor is assessed according to the **R classification**:

- RX = presence of residual tumor cannot be assessed
- R0 = no residual tumor
- R1 = microscopic residual tumor (positive resection margin)
- R2 = macroscopic residual tumor

Therapy and Prognosis of Gastric Cancer

Standard therapy for gastric cancer is the complete surgical resection - R0 - of the tumor. In most cases, R0 resection means performing a gastrectomy; the total removal of the stomach to include the greater and lesser omentum and the lymph nodes. Smaller, early cancers that are limited to the mucosa are suitable for endoscopic removal as well. Starting with stage T3, multimodal therapy, consisting of perioperative chemotherapy and surgical intervention, is recommended.

In cases of gastroesophageal junction cancers, a distal esophagus resection is additionally performed. In later stages, once the tumor has already metastasized, the attempt is made to extend survival through palliative chemotherapy.

The prognosis of gastric cancer largely depends on the stage the tumor is at the time of diagnosis. Carcinoma in situ has a five-year survival rate of 100% and, with regard to pT1N1M0 and pT2N0M0; it is still at 70%. In all advanced stages, the deciding factor is how resectable the tumor is. If R0 resections have a five-year survival rate of up to 45%, this rate decreases to almost zero with R1 and R2 resections!

Note: Following a gastrectomy, patients receive nutritional counseling. Furthermore, they will have to substitute Vitamin B12 and pancreatic enzymes for the rest of their lives.

Other Gastric Tumors

Benign gastric tumors

Benign gastric neoplasms (polyps, cysts, hamartoma) are often found incidentally and are usually asymptomatic. They are rarer than malignant neoplasms and do not have the ability to infiltrate or metastasize. If they grow expansively, dysphagia, bleeding, and symptoms of pyloric stenosis may occur, depending on the location of the tumor. Therapy options consist of endoscopic or surgical removal of the tumor.

Gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumors are mesenchymal sarcomas that frequently occur in the stomach and small intestine. It is unusual to find GIST located outside the stomach, i.e. in the omentum or peritoneum, in which case they have a far more negative prognosis.

The incidence of GIST is 1/100.000 annually. The GIST diagnosis is confirmed via imaging procedures, such as CT, MRT and PET scans, as well as a biopsy to provide histological findings. 90% of these tumors express the antigen CD117, which is part of the c-KIT receptor. Therapy and prognosis of GIST significantly depend on the size of the tumor and its mitotic index.



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Small R0 resectable tumors that may have been treated with neoadjuvant therapy have a good chance of healing. Inoperable GISTs are preferably treated with the tyrosine kinase inhibitor, such as imatinib. These tumors develop hepatic and peritoneal metastases. Most gastrointestinal stromal tumors are found incidentally due to their non-specific vague symptoms, in some cases, there may be bleeding.

Other tumors may affect the stomach as well, i.e. the **MALT lymphoma**, which is considered to be part of the non-Hodgkin lymphomas.

Review Questions

The answers are below the references.

1. Which statement is not true? Symptoms of gastric cancer may be:

- A. In the advanced stage of gastric cancer, the Virchow's lymph node can be palpable.
- B. Malignant acanthosis nigricans (acanthosis nigricans maligna), a cutaneous paraneoplastic syndrome, frequently occurs in the early stages of the disease.
- C. Pyloric stenosis and bleeding are complications due to tumor growth.
- D. A sudden aversion to meat may be an indicator of gastric cancer.
- E. Gastric cancer causes only non-specific symptoms in the beginning stages.

2. Which statement is not true? Causes of gastric cancer may be:

- A. The biggest risk for gastric cancer is gastroduodenal ulcer disease.
- B. An infection with *Helicobacter pylori* is a frequent cause of gastric cancer.
- C. Partial gastrectomy poses a certain risk of degeneration.
- D. Adenomatous gastric polyps may degenerate.
- E. Giant fold gastritis may be a cause of gastric cancer.

3. Which statement regarding metastasizing gastric cancer is not true?

- A. 70% of patients have already developed lymph node metastases at the time of diagnosis.
- B. Gastric cancer metastasizes early on to the lymph nodes of the lesser and greater curvature.
- C. The Krukenberg tumor is a metastasis of gastric cancer in the ovaries or the pouch of Douglas.
- D. Per continuitatem, the tumor metastasizes into the esophagus, duodenum, colon, and pancreas.
- E. The hematogenous spread to the liver, lungs, bones, and brain takes place during the early stages of the disease.

References

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Correct answers: 1B, 2A, 3E

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